AR201-13972

Jodi Burgess
09/26/2002 09:38 AM

To:
cc:
cc:
Subject: Test Plan and Summaries for Aromatic Terpene Hydrocarbons

----- Forwarded by Ralph Northrop/DC/USEPA/US on 09/26/02 09:01 AM -----

"Adams, Tim" <tadams@therobertsgroup.net> on 06/26/2002 09:42:04 AM

To: "chem.rtk@epa.gov" <oppt.ncic@epa.gov,>
cc:
Subject: Submission of Test Plan and Robust Summaries for Aromatic Terpene Hydrocarbons

Dear:Ms. Whitman:

On behalf of the Flavor and Fragrance High Production Volume Consortia (FFHPVC), I wish to submit the submission letter, test plan and robust summaries for the chemical category designated as the "Aromatic Terpene Hydrocarbons".
The test plan and robust summaries are submitted in pdf. files. We will provide you with a hard copy of these documents upon request .

If there is a problem with the electronic transfer of these files, please feel free to contact me at any time.
Respectfully,
Timothy B. Adams Ph.D.
Technical Contact Person for FFHPVC

<<Submission Letter for Aromatic Terpene Hydrocarbons.doc>> <<Test Plan for Aromatic Terpene Hydrocarbons.pdf>> <<Robust Summaries for Aromatic Terpene Hydrocarbons.pdf>>

Submission Letter for Aromatic Terpene Hydrocarbo

Test Plan for Aromatic Terpene Hydrocarbon

Robust Summaries for Aromatic Terpene Hydrocarbc

The Flavor and Fragrance High Production Volume Consortia
(FFHPVC)
1620 I Street, N.W.
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Washington D.C. 20006
Tel. (202)-331-2325 Fax (202)-463-8998

June 26, 2002

Christie Todd Whitman, Administrator
US EPA
P.O. Box 1473
Merrifield, VA 22116
Attn: Chemical Right-to-Know Program

Dear Ms. Whitman:

On behalf or the member companies of the Terpene Consortium, the Flavor andFragrance High Production Volume Consortia is pleased to submit the Test Plan andRobust Summaries for the chemical category designated the "Aromatic Terpene Hydrocarbons" to the HPV Challenge Program, AR-201. The Terpene Consortium has chosen not to belong to the HPV Tracker System for submission of test plans and robust summaries. We are therefore submitting the test plan and accompanying robust summaries directly to EPA to make available to the public. This submission includes one electronic copy in pdf. format. A hard copy of this submission is available upon request. The EPA registration number for the Terpene Consortium is

Please feel free to contact me with any questions or comments you might have concerning the submission at tadams@therobertsgroup.net, tadams@chemintox.com or 202-331-2325.

Sincerely,
Timothy Adams, Ph.D.
Technical Contact Person for FFHPVC

AR201-13972A

The Flavor and Fragrance High Production Volume Consortia

The Terpene Consortium

Test Plan for Aromatic Terpene Hydrocarbons

p-Cymene CAS No. 99-87-6

FFHPVC Terpene Consortium Registration Number

Submitted to the EPA under the HPV Challenge Program by:

The Flavor and Fragrance High Production Volume Chemical Consortia

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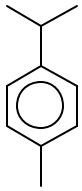
The Flavor and Fragrance High Production Volume Consortia

Test Plan for Aromatic Terpene Hydrocarbons

1 Identity of Substances



***p*-Cymene**

CAS No. 99-87-6

Synonyms: *p*-Methylcumene
4-Methylisopropylbenzene
p-Methylisopropylbenzene
p-Isopropyltoluene

2 Category Analysis

2.1 Introduction

In October of 1999, members of the U.S. flavor and fragrance industries as well as other manufacturers that produce source materials used in flavors and fragrances formed consortia of companies in order to participate in the Chemical Right-to-Know Program. Members of these consortia are committed to assuring the human and environmental safety of substances used in flavor and fragrance products. The consortia are organized as the Flavor and Fragrance High Production Volume Consortia (FFHPVC). The terpene consortium, as a member of FFHPVC, serves as an industry consortium to coordinate testing activities for terpene substances under the Chemical Right-to-Know Program. Twenty-one (21) companies are current members of the Terpene Consortium. The Terpene Consortium and its member companies are committed to assembling and reviewing available test data, developing and providing test plans for each of the sponsored chemicals, and where needed, conducting additional testing. The test plan, category analysis and robust summaries presented represent the first phase of the Consortium's commitment to the Chemical Right-to-Know Program.

2.2 Background Information

This category analysis and test plan provides data for *p*-cymene and other structurally related aromatic terpene hydrocarbons. *p*-Cymene is currently permitted by the U.S. Food and Drug Administration (FDA) for direct addition to food for human consumption as a flavoring substances and is considered by the Flavor and Extract Manufacturers' Association (FEMA) Expert Panel to be "generally recognized as safe" (GRAS) for its intended use as a flavoring substance [Hall, 1960]. *p*-Cymene occurs naturally in more than 200 foods [CIVO-TNO, 2000]. Quantitative natural occurrence data indicate that oral intake of *p*-cymene occurs predominantly from consumption of foods such as butter, carrots, nutmeg, orange juice, oregano, raspberries, and lemon oil, and almost every spice [Stofberg and Grundschober, 1987]. It has been estimated that approximately, 30,000 kg of *p*-cymene is consumed annually

as a natural component of butter, carrots, lemon oil, orange juice, oregano, and raspberry [Stofberg and Grundschober, 1987]. Based on more recent and extensive natural occurrence data [CIVO-TNO, 2000] and annual volume of use data [Lucas *et al.*, 1999; Lawrence, 1985] intake of *p*-cymene from consumption of traditional food approaches 100,000 kg.

2.3 Structural Classification

This chemical category contains aromatic terpene hydrocarbons. *p*-Cymene is a C_{10} terpene hydrocarbon that is recognized chemically as *p*-methylisopropylbenzene. As a terpene hydrocarbon, it is closely related in structure to another naturally occurring plant component, cumene or isopropylbenzene. Based upon the similarity in physical properties, chemical reactivity, and pharmacokinetic and metabolic data, *p*-cymene and cumene represents the chemical category designated aromatic monoterpene hydrocarbons.

2.4 Industrial and Biogenic Production

Crude sulfate turpentine (CST) is a complex mixture of C_{10} monoterpene hydrocarbons composed mainly of *alpha*-pinene (60-65%), *beta*-pinene (25-35%) and other monocyclic terpenes such as limonene (2-4%) and *p*-cymene (0.2%). It has been estimated that the worldwide production of turpentine is approximately 330,000 metric tons of which almost 100,000 metric tons is gum turpentine and the bulk of the remainder is sulphate turpentine [National Resources Institute, 1995]. In 1977, the annual United States production of CST and wood turpentine was reported to be 92,750 and 9,150 tons, respectively [McKibben, 1979]. The annual amount of *p*-cymene present in CST used in the United States is approximately 20 metric tons (20,000 kg).

Level-three fugacity calculations indicate that the environmental distribution of turpentine and its components is essentially entirely into the air [Mackay, 1996a, 1996b]. If it were conservatively assumed that through the various industrial processes approximately 2% is lost, the total annual worldwide emission of *p*-cymene from turpentine would be 400 kg. This can be compared with the biogenic emissions into the air discussed below.

As an important plant terpene hydrocarbon, *p*-cymene is an important component of the earth's atmosphere [Guenther *et al*., 2000]. *p*-Cymene is relatively volatile and widely distributed in plants, especially conifers [Helmig *et al.*, 1999a]. Measurements of emissions from sixty-three vegetation species in this study reported the occurrence of *p*-cymene so commonly as to lead to the conclusion that *p*-cymene is practically ubiquitous in plants. In determining the impact on the environment of the industrial production and use *p*-cymene, it is also important to examine the impact as a result of emissions from biogenic sources [Guenther *et al*., 2000].

Landscape flux potentials of *p*-cymene have been measured in three quite varied sites (an urban forest, a mixed deciduous and coniferous forest, and a mixed shrub oak forest) in the U.S. from each of 63 species of trees [Helmig *et al*., 1999a, 1999b]. *p*-Cymene was detected in a substantial proportion of the species measured with fluxes ranging from 0.1 to 7 $\mu gChr^{-1}gdw^{-1}$ (µg carbon per hour per gram dry weight) [Helmig *et al.*, 1999a]. These fluxes have been used to calculate average hourly fluxes for each substance at each site [Helmig *et al.*, 1999b]. For *p*-cymene these were 88, 54 and 8 $\mu gCm^{-2}hr^{-1}$ (µg carbon per m^2 per hour). These emissions of *p*-cymene amounted to 4.4, 1.2 and less than 0.2% of the total volatile organic compounds (VOC) emissions for each of the three sites, respectively. These figures can be used to estimate the total global emissions of these materials (see below).

In a recent review of natural emissions of volatile compounds [Guenther *et al*., 2000] it was estimated that in North America the total annual emission of for *p*-cymene was 1.1 million metric tons. The total global emissions of *p*-cymene can be estimated in two ways. The total annual global emission of VOCs has been estimated as 1150 million metric tons [Guenther *et al*., 1995]. If the same percentage of total emissions of VOCs as has been measured over 3 different forest types, 4.4, 1.2 and less than 0.2% (average = 1.9%) are used, it can be estimated that the total annual global emissions for *p*-cymene would be approximately 22 million metric tons. On the other hand, if the average rates of emission of *p*-cymene (50 $\mu gCm^{-2}hr^{-1}$) (average of 88, 54 and 8 $\mu gCm^{-2}hr^{-1}$), *beta*-pinene (22 $\mu gCm^{-2}hr^{-1}$) and camphene (58 $\mu gCm^{-2}hr^{-1}$) are applied to the latest global forest coverage estimates of 3.9 billion hectares [Food and

Agriculture Organization, 2000], then annual global biogenic emissions of *p*-cymene is approximately 17.2 million metric tons can be calculated.

Based on the above estimates, it can be concluded that total annual atmospheric emission of *p*-cymene is predominantly from biogenic sources (17,200,000 kg/yr of biogenic emissions *versus* 400 kg/yr of anthropogenic emissions). The relative contribution from biogenic and industrial sources can be represented by a global emission ratio (GER = biogenic emission/industrial emission). In the case of *p*-cymene, the GER would exceed 1,000, suggesting that biogenic emissions far exceed man-made emissions. As a result, humans are unavoidably exposed to the naturally occurring aromatic terpene hydrocarbon *p*-cymene.

2.5 Metabolism of *p*-Cymene and Cumene

The metabolism of *p*-cymene has been studied *in vivo* using rats, rabbits, guinea pigs, brushtail possums, greater gliders (*Petauroides volans*), and ringtail possums [Boyle *et al*., 1999; Matsumoto *et al*., 1992; Walde *et al*., 1983; Bakke and Scheline, 1970]. The pharmacokinetics, metabolism and distribution of cumene has been studied in rabbits and rats [Research Triangle Institute, 1989; Robinson *et al.*, 1954; van Doorn *et al.*, 1981]. In general, the studies indicate that *p*-cymene (*p*-methylisopropylbenzene) or cumene (isopropylbenzene) is rapidly absorbed by oral or inhalation routes. They undergo oxidation (hydroxylation) of the side chain isopropyl substituent and, in the case of *p*-cymene, the methyl substituent to yield polar oxygenated metabolites. These metabolites are either excreted unchanged in the urine or undergo Phase II conjugation with glucuronic acid and/or glycine followed by excretion in the urine. Unchanged *p*-cymene or cumene were not detected in the urine or feces.

A dose level of 33 mg/kg bw of [^{14}C]-cumene given to male and female Fischer F/344 rats by either a single intravenous injection, a single oral gavage, or repeated oral gavage for 8 days is rapidly absorbed from the stomach. Rats exposed to atmospheres containing 100, 500 or 1500 ppm for 6 hours show detectable levels of [^{14}C]-cumene within 5 minutes [Research Triangle Institute, 1989]. Tissue distribution data (tissue to blood ratios) indicate that the lipophilic substance is distributed mainly to adipose tissue and those organs responsible for the

metabolism (liver) and excretion (kidneys) of [^{14}C]-cumene. Based on a two compartment open pharmacokinetic model, the distribution half-life of [^{14}C]-cumene is 0.21 and 0.27 hours for male and female rats, respectively, given an intravenous dose of 33 mg/kg bw. The elimination half-life was calculated to be 8.6 and 7.3 hours for males and females, respectively [Research Triangle Institute, 1989].

Regardless of the route of administration, [^{14}C]-cumene is eliminated predominantly in the urine. At lower oral dose levels or lower levels of inhalation exposure, a minimum of 70% is excreted in the urine. Relatively little radioactivity is present in expired air or in the feces at low dose levels. Overall dose levels and routes of administration (oral gavage or inhalation) greater than 50% of the urinary metabolites is accounted for by free or conjugated (glucuronide or sulfate) 2-phenyl-2-propanol, the product of benzylic hydroxylation. Smaller amounts of free or conjugated 2-phenyl-1,2-propanediol and 2-phenylpropionic acid are also present in the urine.

Rabbits given a 1720 mg dose of cumene excrete mainly 2-phenyl-2-propanol (40%) and lesser amounts of 2-phenyl-1-propanol (25%) and 2-phenylpropionic acid (25%) in the urine [Robinson *et al.*, 1954]. 2-Phenyl-2-propanol, 2-phenyl-1-propanol and 2-phneylpropionic acid were detected when 200 mg/L cumene was incubated with freshly prepared rabbit liver soluble enzyme preparation [Chakraborty and Smith, 1967].

Humans exhibit normal background levels of cumene in exhaled air. Levels of 0.35 ng/L of cumene have been measure in the expired air of normal healthy urban men and women [Conkle *et al.*, 1975; Krotoszynski *et al.*, 1977]. Mean environmental levels of 6 ng/L of cumene resulted in mean alveolar, blood, and urine levels of 3, 199, and 202 ng/L in the 49 volunteers [Parbellini *et al.*, 1988]. A comparison of alveolar and blood cumene levels in hospital (58) and chemical workers (28) exposed to environmental concentrations of 6.4 and 10.7 ng/L showed no significant difference in alveolar cumene concentrations. Alveolar cumene retention ranged from 70% in hospital workers to 78% in chemical workers. Lower blood cumene levels in hospital workers were correlated with lower environmental concentrations [Brugnone *et al.*, 1989].

Humans (5 males and 5 females/group) exposed to an atmosphere containing 49, 98, or 147 ppm cumene for 7 hours showed 64% absorption at 0.5 hours and 45% at 7 hours. Maximum excretion is observed at 6 to 8 hours and is essentially complete at 48 hours. Approximately 35% of the dose inhaled was excreted as 2-phenyl-2-propanol [Senczuk and Litewka, 1976].

In conclusion, cumene is rapidly absorbed by oral administration or inhalation exposure. Following absorption, the ring substituent is oxidized to yield aromatic alcohol and carboxylic acid metabolites that are excreted free or conjugated in the urine. There is no evidence that cumene accumulates in the body even following high dose or repeat dose exposure.

Like cumene, *p*-cymene participates in the same metabolic pathways in a variety of species (rat, brushtail possum, greater glider and ringtail possum) [Boyle *et al.*, 1999]. In the rat, the two principle urinary metabolites are formed by benzylic oxidation. Forty-eight (48) hours after an oral dose, 2-*p*-tolypropan-2-ol (34-39% of recovered dose) and 2-*p*-carboxyphenylpropan-2-ol (19-23% of recovered dose) are present in the urine. The former metabolite is the product of benzylic hydroxylation of the isopropyl substituent while the latter metabolite is the product of benzylic hydroxylation of the isopropyl substituent and the methyl substituent. 2-*p*-Carboxyphenylpropan-2-ol is the principle urinary metabolite in the ringtail possum (36% of recovered dose) and 2-*p*-carboxyphenylpropan-1-ol is the principal urinary metabolite in the brushtail possum and greater gilder (56-59% and 42% of recovered dose for brushtail possum and greater glider, respectively). The ringtail possum and greater glider also excrete 2-*p*-carboxyphenylpropionic acid as another principal urinary metabolite (41 and 46% of recovered dose, respectively). The authors noted that rats and brushtail possums excreted metabolites containing 2, 3, 4 oxygen atoms added through oxidation of *p*-cymene; whereas, greater gliders and ringtail possums, which are mammals accustomed to consuming a diet naturally high in terpenes, excreted metabolites containing 3 or 4 oxygen atoms, suggesting a more efficient oxidation system in the latter species.

Both the greater glider and ringtail possum do not excrete detectable amounts of conjugated metabolites. In the rat, a larger percentage of metabolites were conjugated (34.2% free *versus*

65.8% conjugated) when *p*-cymene was orally administered at 0.37 mmol/kg bw (50 mg/kg bw) [Boyle *et al.*, 1999]. However, the percent conjugated was significantly reduced (81.9% free *versus* 18.1% conjugated) when a higher dose of *p*-cymene was administered (1.49 mmol/kg bw [200 mg/kg bw]). In the brushtail possum, percent conjugation was comparable between doses (0.37 mmol/kg bw: 59.9% free *versus* 40.1% conjugated; 1.49 mmol/kg bw: 44.3% free *versus* 55.7% conjugated).

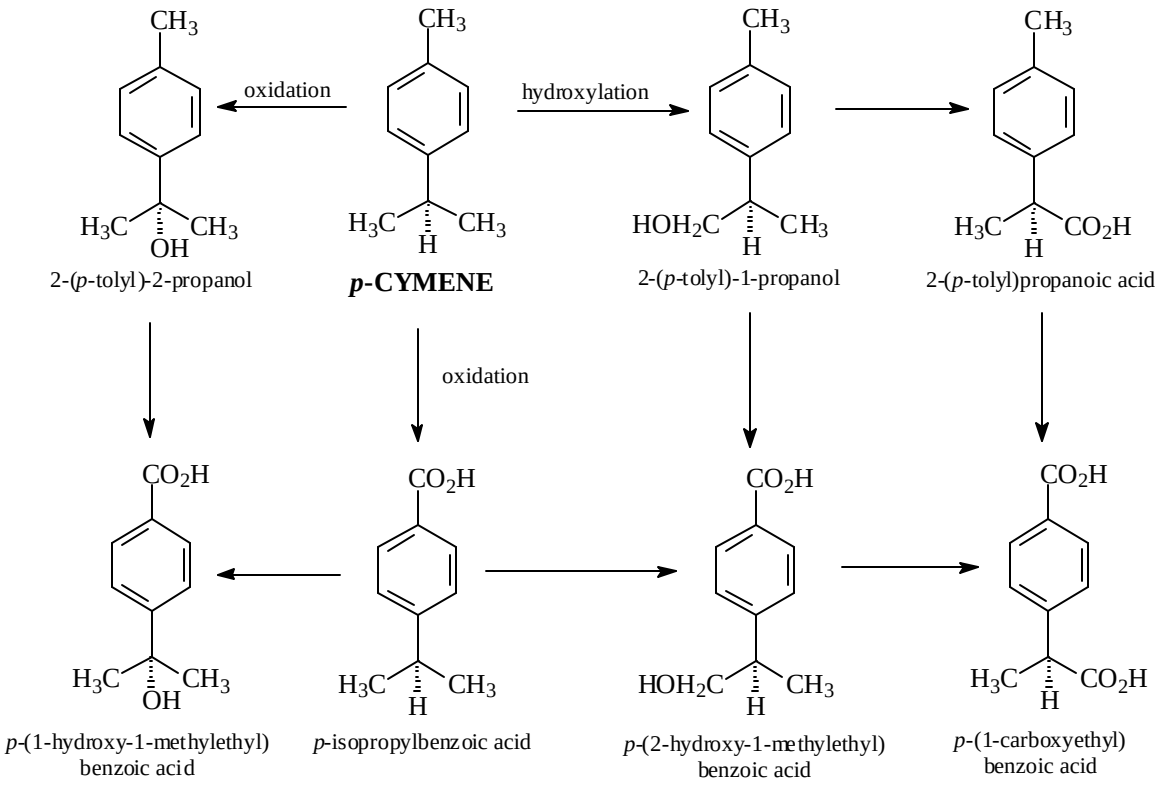
The metabolism of *p*-cymene has been studied in rats and guinea pigs. From 60 to 80 % of an oral or inhaled dose of 100 mg/kg bw of *p*-cymene is excreted in the urine within 48 hours [Walde *et al*., 1983]. As in other studies with cumene and *p*-cymene, the principal metabolites involve oxidation of the side chain substituents. Following oral administration, the principle urinary metabolites were *p*-isopropylbenzoic acid (19%) and 2-*p*-carboxyphenylpropionic acid (16%). Following inhalation exposure, the primary urinary metabolite was 2-*p*-carboxyphenylpropionic acid (15%); *p*-isopropylbenzoic acid was a minor metabolite (9%). Other urinary metabolites in the rat included 2-*p*-tolylpropan-1-ol (oral: 8%; inhalation: 6%), 2-*p*-carboxyphenylpropan-2-ol (oral and inhalation: 9%), 2-*p*-(hydroxymethyl)phenylpropionic acid (oral: 4%; inhalation: 7%), 2-*p*-carboxyphenylpropan-1-ol (oral: 11%; inhalation: 9%), and *p*-isopropylbenzoylglycine (oral: 2%; inhalation: 3%).

In guinea pigs, similar urinary metabolites were identified. The primary urinary metabolite from both oral and inhalation exposure was *p*-isopropylbenzoylglycine (31%) indicating that conjugation with glycine was more prevalent in guinea pigs than in rats. In addition, where no ring hydroxylation of *p*-cymene was reported in rats [Bakke and Scheline, 1970; Walde *et al*., 1983], trace amounts of carvacrol and hydroxycarvacrol were detected in guinea pigs following oral and inhalation exposure [Walde *et al*., 1983].

The metabolism of *p*-cymene also was studied in rabbits following oral administration of approximately 1000 mg/kg of *p*-cymene to four (2M/2F) white rabbits [Matsumoto *et al*., 1992]. Seven (7) metabolites were isolated from urine collected for 3 days after dosing. The oxidation of *p*-cymene occurs stereoselectively. Oxidation of the methyl group of the isopropyl

substituent yields 2-(p-tolyl)-1-propanol in an R/S ratio of 65:35. The (R)-alcohol is then further oxidized to (R)-2-(p-tolyl)propanoic acid which undergoes complete stereochemical inversion to (S)-2-(p-tolyl)propanoic acid. Subsequently, the alcohol or acid metabolite may undergo oxidation of the tolyl methyl group to yield the corresponding hydroxy acid and diacid, respectively. If the tolyl methyl is oxidized before the isopropyl group, no stereochemical inversion is observed when the propanol is converted to the propanoic acid derivative. Based on the observed stereochemical changes, it is evident that *omega*-hydroxylation of *p*-cymene or *p*-isopropylbenzoic acid metabolite occurs preferentially at the *pro-S*-methyl group of the isopropyl substituent. The metabolic pathways of *p*-cymene in rabbits are shown in Figure 1.

Figure 1 - Proposed Metabolic Pathways of *p*-cymene in Rabbits



2.6 Summary for Category Analysis

p-Cymene, a natural component of the diet, and the structurally related homologue cumene are readily absorbed, metabolized and rapidly excreted *via* the urine as free and conjugated polar metabolites. The physiochemical properties and low toxic potential of *p*-cymene and cumene are consistent with their known reactivity and metabolic fate.

3 Test Plan

3.1 Chemical and Physical Properties

3.1.1 Melting Point

The melting point of *p*-cymene has been reported to be –67.94 °C [Merck, 1996; CRC, 1986] and –68 °C [International Programme on Chemical Safety & The Commission of the European Communities, 1993]. Based on these reported values the melting point of *p*-cymene is –68 °C.

3.1.2 Boiling Point

The measured boiling point of *p*-cymene has been reported to be 177 °C [Furnas and Hine, 1958] and between 176 and 177.1 °C in several standard references [International Programme on Chemical Safety & The Commission of the European Communities, 1993; FMA; CRC, 1986; Merck, 1996]. Based on the consistency of these values, the boiling point of *p*-cymene is 176-177 °C.

3.1.3 Vapor Pressure

The vapor pressure of *p*-cymene has been reported to be 1.50 mm Hg (200 Pa) at 20 °C [International Programme on Chemical Safety & The Commission of the European Communities, 1993] and 1.46 mm Hg (194 Pa) at 25 °C [Mackay *et al.*, 1982]. The calculated vapor pressure for *p*-cymene according to the MPBPWIN program was 1.11 mm Hg (148 Pa) at 25°C [MPBPVP EPI Suite, 2000]. Based on these data the vapor pressure is approximately 1.50 mm Hg (200 Pa) at 20 °C.

3.1.4 Octanol/Water Partition Coefficients

The octanol/water partition coefficient for *p*-cymene was measured using GC analysis. The log KOW was reported to be 4.1 at 23±1.5 °C [Banerjee *et al*., 1980]. Log KOW was also calculated resulting in values of 4.0 [KOWWIN EPI Suite, 2000] and 4.19 [Interactive

Analysis LogP and LogW Predictor]. The close agreement between measured and calculated values indicated that the log KOW for *p*-cymene is 4.1.

The calculated log KOW of cumene that is expected to be more water soluble than *p*-cymene is 3.63 [Mackay *et al*., 1980].

3.1.5 Water Solubility

The water solubility of *p*-cymene was measured using GC analysis and reported to be 23.35 mg/L at 25°C in distilled water [Banerjee *et al*., 1980] and 20 mg/L at 25 °C [International Programme on Chemical Safety & The Commission of the European Communities, 1993]. Water solubility was also calculated resulting in a value of 11.675 mg/L [Interactive Analysis LogP and LogW Predictor]. Water solubility of cumene in synthetic seawater (500 mg/L at 25°C) is expected given the log KOW of this more polar substance (log KOW=3.63) [Price *et al*., 1974].

3.1.6 New Testing Required

None.

3.2 Environmental Fate and Pathways

3.2.1 Photodegradation

The calculated half-life value for *p*-cymene has been reported to be 15.03 hours [AOPWIN EPI Suite, 2000]. The fact that *p*-cymene contains a reactive benzylic hydrogen capable of reaction with hydroxyl and peroxy radicals supports the calculated short half-life.

3.2.2 Stability In Water

No hydrolysis is possible for any of the materials in this group. All are expected to be very stable in aqueous solution.

3.2.3 Biodegradation

The structurally related compound, cumene, was tested for biodegradation in freshwater and synthetic seawater using a standard biochemical oxygen demand (BOD) procedure. Percent bio-oxidation was the difference between the cumulative oxygen uptake for oxidation of the carbonaceous material in the test sample bottle and the cumulative oxygen uptake in a blank. In freshwater, cumene was considered by the authors to be inherently biodegradable showing 70% bio-oxidation within 20 days. Conversely, in synthetic seawater, cumene was considered not biodegradable showing virtually no bio-oxidation (2%) after 20 days [Price *et al.*, 1974].

It is recommended that *p*-cymene be subjected to a biodegradability study according to a standard OECD Guideline protocol.

3.2.4 Fugacity

Transport and distribution in the environment were modeled using Level III Fugacity-based Environmental Equilibrium Partitioning Model [Mackay, 1991a, 1996b] through the EPA EPI suite 2000 program. The input parameters used were molecular weight, measured melting point (-67.94 °C), vapor pressure (1.46mm Hg), water solubility (23.4 mg/L), and log KOW (4.10).

The model predicts that *p*-cymene is distributed mainly to the soil (65.3%), but also is distributed to water (27.7%) and, to some extent, air (4.73%) and sediment (2.22%).

The significance of these calculations must be evaluated in the context that *p*-cymene is a product of plant and animal biosynthesis and is, therefore, ubiquitous in the environment. The model does not account for the influence of biogenic production on partitioning in the environment nor does it take into account any biodegradation.

3.2.5 New Testing Required

- Biodegradation study of *p*-cymene according to OECD Guideline protocol.

3.3 Ecotoxicity

3.3.1 Acute Toxicity to Fish

Suitable measured and calculated fish LC50s are available for *p*-cymene and its structural relative, cumene. Sheepshead minnows were used to determine LC50 of *p*-cymene at time intervals up to 96 hours in a static test [Heitmuller *et al*., 1981]. At 24, 48, 72, and 96 hours, the LC50s were 56, 50, 48, and 48 ppm, respectively, with a no-observed-effect concentration (NOEC) of 10 ppm. The calculated 96-hour LC50 was reported to be 1.056 mg/L (neutral organics) and 0.668 mg/L (SW) and 14-day LC50 was reported to be 2.671 mg/L [ECOSAR EPI Suite, 2000].

Sheepshead minnows were used to calculate LC50 of cumene at time intervals up to 96 hours in a flow-through system [Glickman *et al*., 1995]. At 24, 48, 72, and 96 hours, the LC50s were 8.1, 5.7, 4.8, and 4.7 mg/L, respectively, with a NOEC of less than 2.9 mg/L. Similarly, LC50s were calculated using rainbow trout. At 24, 48, 72, and 96 hours, the LC50s were 6.4, 5.8, 5.2, and 4.8 mg/L, respectively, with a NOEC of 1.9 mg/L. The authors concluded that cumene is moderately toxic to fish but cumene's high volatility would limit its toxicological impact to an aquatic environment. The 96-hour LC50 of cumene in red killifish was determined to be 18 mg/L following OECD Guideline 203 [Yoshioka and Ose, 1993].

Given the current database of information, it will not be necessary to perform additional acute fish toxicity tests for this endpoint.

3.3.2 Acute Toxicity to Aquatic Invertebrates

Measured and calculated aquatic invertebrate LC50s are available for *p*-cymene and its structural relative, cumene. In *Daphnia magna*, the LC50 of *p*-cymene was determined to be 9.4 and 6.5 mg/L at 24 and 48 hours, respectively, with a NOEC of less than 4.6 mg/L in a static test [LeBlanc, 1980]. In addition, calculated values were reported for 48-hour LC50 of 1.309 mg/L and a 16-day EC50 of 0.168 mg/L [ECOSAR EPI Suite, 2000]. A calculated 96-hour LC50 of 0.068 mg/L was reported for mysid shrimp [ECOSAR EPI Suite, 2000].

Mysid shrimp were used to determine LC50 of cumene at time intervals up to 96 hours in a flow-through system [Glickman *et al*., 1995]. At 24, 48, 72, and 96 hours, the LC50 were greater than 2.0, 1.6, 1.4, and 1.3 mg/L, respectively, with a NOEC of 0.68 mg/L. Similarly, LC50 were calculated using *Daphnia magna*. At 24 and 48 hours, the LC50 were 4.8 and 4.0 mg/L, respectively, with a NOEC of 1.5 mg/L. The authors concluded that cumene is moderately toxic to invertebrates but cumene's high volatility would limit its toxicological impact to an aquatic environment. The median tolerance limit of cumene was determined to be 110 mg/L in a static test using brine shrimp (*Artemia salina*) over a period of 24 hours [Price *et al*., 1974].

Given the current database of information, it will not be necessary to perform additional acute fish toxicity tests for this endpoint.

3.3.3 Acute Toxicity to Aquatic Plants

A calculated 96-hour EC50 of 0.923 mg/L was reported for green algae [ECOSAR EPI Suite, 2000]. It is recommended that *p*-cymene be subjected to acute toxicity test in green algae.

3.3.4 New Testing Required

- Acute toxicity to algae according to OECD guideline 201 for *p*-cymene

3.4 Human Health Toxicity

3.4.1 Acute Toxicity

As described below, mammalian LD50 for *p*-cymene have shown it to have low toxic potential. Similar studies with cumene have concurred with these results. Oral LD50s in rats of 2,990-4,750 mg/kg bw and a dermal LD50 in rabbits of greater than 5,000 mg/kg bw have been reported [MacDonald, 1961, 1962a; Jenner *et al*., 1964; Moreno, 1973; Smyth *et al*., 1951].

Inhaled *p*-cymene at an atmospheric concentration of 9.7 mg/L over a period of 5 hours was reported to be irritating to rats and guinea pigs [MacDonald, 1962b]. Within 15 (rats) and 90

(guinea pigs) minutes, transient clonic convulsions were reported. However, these effects were fully reversible by the following morning. In mice, this same exposure scenario resulted in similar effects; however, two mice died during exposure and the third mouse died during the night [MacDonald, 1962b]. Necropsies of the mice showed hyperemic lungs, mottled liver, and pale kidneys.

The oral LD50 of cumene in rats was reported to be 1,400-2,910 mg/kg bw and the dermal LD50 in rabbits was reported to be 10,545 mg/kg bw [Smyth *et al*., 1951; Wolf *et al*., 1956]. In an inhalation study, rats were exposed to an atmosphere containing liquid cumene suspended at a concentration of 8,000 mg/L for 4 hours. Animals were observed for 14 days. Four (4) of 6 rats died [Smyth *et al*., 1951].

Single exposure to inhaled cumene at concentrations up to 1,200 ppm for 6 hours was reported to produce reversible alterations (within 24 hours post-exposure) in the functional observational battery one hour post-exposure [Cushman *et al*., 1995].

Rats exposed to atmospheres containing 5,000 to 10,000 ppm cumene for four exposures of 30, 20, 45, and 50 minutes duration resulted in local irritation, depression, and quivering or twitching [Furnas and Hine, 1958]. At necropsy, no gross or microscopic effects were reported other than those associated with respiratory irritation.

Given the numerous studies available, additional acute toxicity tests in mammals are not recommended.

3.4.2 *In vitro* and *In vivo* Genotoxicity

3.4.2.1 In vitro

p-Cymene produced no increase in the frequency of mutations when tested in Sd-4-73 *Escherichia coli* [Szybalski, 1958]. Concentrations up to 2,000 µg/plate of cumene did not increase the number of revertants in *Salmonella typhimurium* strains (TA97, TA98, TA100,

TA1535, and TA1537) in the Ames preincubation assay with or without metabolic activation [NTP unpublished results (e); Lawlor and Wagner, 1987].

In cultured mammalian cells, cumene showed no consistent evidence of mutagenicity or genotoxicity at non-cytotoxic concentrations. Cumene did not increase mutations in the CHO/HGPRT test with or without metabolic activation at concentrations of up to 175 µg cumene/plate [Papciak, 1985; Yang, 1987]. Cultured rat hepatocytes treated with cumene up to 5,000 µg/ml showed cytotoxicity at concentrations of 128 µg/ml and higher and unscheduled DNA synthesis was reported at 16 µg/ml; however, the results between triplicates were highly variable and inconsistent [Brecher, 1984a]. In another study, cultured mouse fibroblasts treated with up to 90 µg/ml of cumene showed cytotoxicity at concentrations of 60 µg/ml and higher [Brecher, 1984b]. At non-cytotoxic concentrations, no increase in cell transformations was reported. No evidence of an increase in the incidence of chromosomal aberration was reported when Chinese hamster ovary cells were incubated with concentrations of cumene up to and including 156 ug/ml with or without metabolic activation [Putnam, 1987].

3.4.2.2 In vivo

In a study conducted by the National Toxicology Program, male F344 rats were intraperitoneally injected with cumene and bone marrow cells were sampled 24 hours following treatment [NTP, 1994]. The authors reported a positive polychromatic erythrocyte trend of P = 0.011; however, minimal dose-response was observed and deaths occurred at the highest dose of 2500 mg/kg bw. Since weakly positive results were reported in this study, a follow-up study was conducted using similar doses [NTP, 1995]. A positive polychromatic erythrocyte trend of P = 0.085 also was reported and the authors concluded that cumene weakly induced micronuclei in F344 rats. Again, a lack of dose-response was observed. Conversely, when cumene was administered to Swiss mice by gavage at doses of up to 1,000 mg/kg bw/day for 2 consecutive days, examination of bone marrow cells showed no induction of micronuclei in either males or females [Khan, 1985].

3.4.2.3 Conclusions

The genotoxicity database on *p*-cymene and cumene shows no mutagenic potential in the Ames assay. In cytogenetic assays, there is no evidence of a genotoxic potential *in vitro*. In whole animals, the genotoxicity results for cumene are mixed showing weakly positive results in micronuclei induction in rats, but no evidence of genotoxicity in mice. Based on these results no additional genotoxicity tests are recommended.

3.4.3 Repeat Dose Toxicity

3.4.3.1 *Subacute Studies*

Groups of 7 to 12 male rats were exposed to 0, 50, or 250 ppm of *p*-cymene for 6 hours/day, 5 days/week for 4 weeks with an 8-week recovery period [Lam *et al*., 1996]. This study was designed to specifically examine the neurotoxic potential of inhaled *p*-cymene. However, a variety of general toxicity parameters were monitored. After the 8-week recovery period, rats were decapitated and the cerebellum was removed, weighed, and homogenized. The remainder of the brain was also weighed and homogenized. Synaptosomes were prepared using gradient centrifugation. The 2 homogenates and the synaptosomes were processed for neurotransmitter analyses (i.e., determination of noradrenaline [NA], dopamine [DA], and 5-hydroxytryptamine [5-HT]), and aliquots were taken for determination of enzyme activities (lactate dehydrogenase [LDH], acetylcholinesterase [AChE], and butylcholinesterase [BuChE]) and protein analysis.

The authors reported that there was no overt toxicity in the treated rats and no effect on body weight or terminal weight of the brain, cerebellum or whole brain. There was also no effect on regional enzyme activities, regional protein synthesis or regional neurotransmitter concentrations. The relative yield and total amount of synaptosomal protein were significantly reduced at 50 and 250 ppm in a concentration-related manner. The relative activity of LDH, AChE, and BuChE were significantly increased at 50 and 250 ppm. Total activity of LDH, AChE and BuChE were unaffected. In relation to the cytoplasmatic marker (LDH), the relative synaptosomal choline esterase activities (AChE and BuChE) and synaptosomal concentrations of NA, DA, and 5-HT

were unaffected by *p*-cymene exposure. Relative to synaptosomal protein, relative NA and DA concentrations were significantly increased at 50 and 250 ppm, whereas 5-HT was unaffected. Conversely, the total amount of NA and DA in the synaptosomal fraction was unaffected by treatment, whereas, the total amount of 5-HT was significantly decreased at 250 ppm. At up to 250 ppm, *p*-cymene exposure did not produce signs of overt toxicity in male rats exposed for 4 weeks with an 8-week recovery period. Although, changes were reported in the synaptosomal fraction of homogenized brain, no generally accepted test system has been established for predicting neurotoxicity based on these measured parameters. Therefore, the results of the above measurements are not indicative of toxicity.

Cumene has been tested by the National Toxicology Program (NTP) in both rats and mice. Animals were exposed to up to 4,000 ppm cumene by whole-body inhalation for 12-13 days over a period of 16-17 days [NTP unpublished results (c, d)]. In rats, all animals died at 4,000 ppm, and about half the animals died at the next exposure concentration (2,000 ppm). Varying degrees of ataxia were reported in surviving rats exposed to 500 to 2,000 ppm cumene. Increased relative liver and kidney weights were reported in rats exposed to cumene. In exposed male rats, hyaline droplets in the renal cortical tubules were reported. At 2,000 ppm, superlative inflammation of the lung was reported in 40% of the rats. In mice, all animals died at the 2 highest exposures (2,000 and 4,000 ppm). At 1,000 ppm, 80% of the female mice died and male mice showed varying degrees of ataxia. Increased relative liver and kidney weights were reported in mice exposed to cumene. Decreased thymus weight was reported in male mice exposed to 1,000 ppm of cumene. No histopathological findings accompanied the organ weight changes. A NOAEL of 1,000 ppm was determined for female rats and male mice and a NOAEL of 500 ppm was determined for female mice based on mortality and histopathological findings.

3.4.3.2 Subchronic Studies

In a continuation of the NTP studies, rats and mice were exposed to concentrations of up to 1,000 ppm cumene by whole-body inhalation 6 hours/day, 5 days/week for up to 13 weeks

[NTP unpublished results (a, b)]. All animals survived to study termination with the exception that 80% of female mice exposed to 1,000 ppm of cumene died. In rats, reported effects included mild ataxia in high-exposure animals, increased relative liver and kidney weights, decreased alanine aminotransferase, and increased hyaline droplet formation and tubular regeneration in renal cortical tubules and granular casts in tubules in the corticomedullary junction area of male rat kidneys. The renal lesions reported in the male rats were considered by the conducting laboratory to be similar to those "resulting from exposure to chemicals that induce accumulation of *alpha*-2µ-globulin in renal cortical tubular cytoplasm". Other terpene hydrocarbons including limonene and camphene have been reported to produce *alpha*-2µ-globulin-induced nephrotoxicity in male Fisher 344 rats. This phenomenon is specific to Fisher 344 male rats and has not been observed in other sexes or strains of rats, other rodents, nor in humans [EPA, 1991a]. In mice, the reported effects included transient ataxia, decreased final body weight of male mice at the 2 highest exposures, increased relative liver weight, centrilobular hypertrophy of the liver in all high-dose males, and squamous hyperplasia and inflammation of the mucosa of the forestomach in females exposed to 500 and 1,000 ppm. A NOAEL of 125 and 250 ppm was determined for rats and mice, respectively, based on serum chemistry, organ weight changes, and histopathological findings.

Two inhalation studies were conducted on cumene using rats. In the first study, rats were exposed to 100 to 1,200 ppm cumene 6 hours/day, 5 days/week for 13 weeks plus 2 or 3 days. The second study included a 4-week recovery period. No animals died during the 13-week study. Reported effects predominantly in the two highest exposure levels (500 and 1,000 ppm) included ataxia, hypoactivity, decreased total motor activity in males, increased water consumption, increased leukocytes and platelets, increased lymphocytes (males only), decreased blood glucose (females only), increased total protein, albumin, globulin, calcium and inorganic phosphorus, increased absolute and relative liver, kidney, and adrenal gland weights, increased tubular proteinosis, interstitial nephritis and tubular cell hyperplasia/hypertrophy in kidneys of males, and increased hyaline droplet formation within the proximal tubules of males. In a review of these data performed by the Environmental Protection Agency (EPA) in 1997, it

was concluded that the kidney effects were related to *alpha*-2μ-globulin-induced nephrotoxicity. The changes in liver weight were considered by EPA not to be toxicologically significant because they were not accompanied by an evidence of histopathology. It was also concluded that the NOAEL in the study is 496 ppm and the LOAEL is 1,202 ppm. The blood effects reported were also considered irrelevant since they were within normal ranges [Cushman *et al.*, 1995].

Other inhalation studies on cumene in a variety of animal species: rats, guinea pigs, dogs and monkeys have been conducted [Jenkins *et al.*, 1970]. In these studies, cumene exposure lasted from 6 weeks (244 ppm cumene) to 90 days (up to 30 ppm cumene) and no statistical analysis was conducted. The only notable effect in the rat studies was an increase in the number of leukocytes, which is consistent with the results discussed above. In guinea pigs, only reduced body weight gain was reported. Increased leukocyte count, and increased hemoglobin and hematocrit were reported in dogs during the 6-week study; however, these effects were not repeated at the 30 ppm in the 90-day study. Monkeys treated for 6 weeks at 244 ppm of cumene showed no adverse effects but during the 90-day study, terminal body weights were lower in treated animals than in controls.

In the only oral toxicity study on cumene, rats were gavaged with cumene up to 769 mg/kg bw/day, 5 days/week for a period of 6 months [Wolf *et al.*, 1956]. Following necropsy and hematological examination, the only effect reported was an increase in average kidney weight (not specified if absolute or relative weight) in the 2 highest dose groups (no statistical analysis). This finding was not accompanied by histopathological renal changes. In all probability the kidney weight changes may be early indications of species and sex specific *alpha*-2μ-globulin-induced nephrotoxicity.

3.4.3.3 Chronic Studies

The US Environmental Protection Agency [EPA, 1997] and the Spanish government [Ministerio de Sanidad Y Consumo, 1997] have conducted risk assessments on cumene. In the EPA assessment, it was noted that the longest study conducted on cumene was that of Wolf *et*

al. (1956), which was about 7 months in duration, and that this length of study was "insufficient in duration to reveal the fate of the observed alterations in organ weights." However, the EPA did proceed to state that there is "some evidence that suggests this compound may not be likely to produce a carcinogenic response (*i.e.*, numerous genotoxic tests, including gene mutation, chromosomal aberration, and primary DNA damage tests, all but one of which were negative or not reproducible, were conducted)." In addition, EPA noted that cumene does not appear to metabolize to highly reactive chemical species and in terms of metabolism, cumene is analogous to methyl benzene for which a 2-year inhalation study was conducted by NTP [NTP, 1990] and no evidence of carcinogenic activity was reported in either rats or mice [EPA, 1997]. Overall, the EPA concluded "there is not much suspicion that cumene would pose a significant carcinogenic hazard." The Spanish assessment [Ministerio de Sanidad Y Consumo, 1997] also noted the lack of long-term data for cumene, but concluded based on the available data, that there "is at present no need for further information and/or testing or for risk reduction measures beyond which are being applied already."

Given that the only structural difference between *p*-cymene and cumene is the presence of a second alkyl substituent (isopropylbenzene *versus* *p*-methylisopropylbenzene), similar conclusions can be drawn for *p*-cymene, particularly since the pharmacokinetic, metabolic and toxicologic data that are available support this conclusion. Therefore, it is not necessary to conduct additional studies on *p*-cymene.

3.4.4 Reproductive Toxicity

Measurement of reproductive potential of this chemical category was incorporated into a subchronic study in rats. In the subchronic rat study described above, male rats were exposed to atmospheres containing up to 1,200 ppm cumene 6 hours/day, 5 days/week for 13 weeks plus 2 or 3 days [Cushman *et al.*, 1995]. The epididymides of some rats were removed to evaluate sperm count and sperm morphology. In addition, the right testis of each male was frozen and homogenized to count spermatid and evaluate the stages of spermatogenesis. Testicular sperm head and epididymal spermatozoa counts were similar for all groups. One

high-dose rat was reported to have diffuse testicular atrophy. However, the total % of normal epididymal sperm across all treatment groups was greater than 96%, indicating no treatment related effects on epididymal sperm morphology. The slight increase in total head abnormalities noted at 500 ppm were considered by the authors to be irrelevant since no dose-response was observed and when evaluated as percentage of sperm assessed, sperm head abnormalities were infrequent. Given these results and taking into consideration the rapid metabolism and excretion of cumene, the EPA [EPA, 1997] concluded, "cumene has low potential for reproductive toxicity." For this reason plus the developmental data provided below, additional reproductive tests on *p*-cymene are not recommended.

3.4.5 Teratogenicity/Developmental Toxicity

A recent well-conducted developmental toxicity study was conducted with cumene in rats and rabbits. Rats and rabbits were used to assess the potential developmental toxicity of cumene [Darmer *et al*., 1997]. Pregnant rats were exposed to atmospheres containing up to 1,200 ppm of cumene inhalation, 6 hours/day during gestation days 6-15 and pregnant rabbits were exposed at up to 2,300 ppm of cumene 6 hours/day during gestation days 6-18. In rats, reported effects included reduced food consumption, reduced body weight gain, perioral wetness, encrustation, and increased relative maternal liver weight. No statistically significant effects were reported in the fetuses. In rabbits, the reported effects included, death of 2 does at the highest concentration, reduced body weight gain, reduced food consumption, increased incidence of perioral wetness, lung color changes in 33% of high-dose does, and increased relative maternal liver weight. No statistically significant effects were reported in the fetuses. There was a significant increase in the incidence of skeletal and visceral variations; however, they were not exposure related. In reviewing this study, EPA [EPA, 1997] set the maternal NOAEL at 488 ppm in rats based on the significant decrease in body weight gain during exposure and increased relative liver weight. Even at maternally toxic concentrations, exposure to cumene vapor did not produce developmental toxicity in rats. In further review of this study, EPA [EPA, 1991] determined that the changes in gestational parameters of the rabbits, though not significant, were consistent in indicating possible developmental effects and therefore set the

NOAEL in rabbits for both developmental and maternal effects at 1,206 ppm and the LOAEL at 2,297 ppm, respectively (as reported in EPA, 1997). Since both cumene and *p*-cymene exhibit such similar pharmacokinetic and metabolic profiles, and show no evidence of toxicity at levels of exposure similar to those experienced by humans, further teratogenic or developmental testing is not recommended.

3.4.6 New Testing Required

None.

3.5 Test Plan Table

Chemical	Physical-Chemical Properties				
	Melting Point	Boiling Point	Vapor Pressure	Partition Coefficient	Water Solubility
CAS No. 99-87-6 *p*-Cymene	A	A	A	A	A

Chemical	Environmental Fate and Pathways			
	Photodegradation	Stability in Water	Biodegradation	Fugacity
CAS No. 99-87-6 *p*-Cymene	Calc	NA	Test, R	Calc

Chemical	Ecotoxicity		
	Acute Toxicity to Fish	Acute Toxicity to Aquatic Invertebrates	Acute Toxicity to Aquatic Plants
CAS No. 99-87-6 *p*-Cymene	A	A	Calc, Test

Chemical	Human Health Data					
	Acute Toxicity	Genetic Toxicity *In Vitro*	Genetic Toxicity *In Vivo*	Repeat Dose Toxicity	Repro-ductive Toxicity	Develop-mental Toxicity
CAS No. 99-87-6 *p*-Cymene	A	A, R	R	A, R	R	R

Legend	
Symbol	**Description**
R	Endpoint requirement fulfilled using category approach, SAR
Test	Endpoint requirements to be fulfilled with testing
Calc	Endpoint requirement fulfilled based on calculated data
A	Endpoint requirement fulfilled with adequate existing data
NR	Not required per the OECD SIDS guidance
NA	Not applicable due to physical/chemical properties
O	Other

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Tel. (202)-331-2325 Fax (202)-463-8998

June 26, 2002

Christie Todd Whitman, Administrator
US EPA
P.O. Box 1473
Merrifield, VA 22116
Attn: Chemical Right-to-Know Program

Dear Ms. Whitman:

On behalf or the member companies of the Terpene Consortium, the Flavor andFragrance High Production Volume Consortia is pleased to submit the Test Plan andRobust Summaries for the chemical category designated the "Aromatic Terpene Hydrocarbons" to the HPV Challenge Program, AR-201. The Terpene Consortium has chosen not to belong to the HPV Tracker System for submission of test plans and robust summaries. We are therefore submitting the test plan and accompanying robust summaries directly to EPA to make available to the public. This submission includes one electronic copy in pdf. format. A hard copy of this submission is available upon request. The EPA registration number for the Terpene Consortium is .

Please feel free to contact me with any questions or comments you might have concerning the submission at tadams@therobertsgroup.net, tadams@chemintox.com or 202-331-2325.

Sincerely,
Timothy Adams, Ph.D.
Technical Contact Person for FFHPVC

AR201-13972B

The Flavor and Fragrance High Production Volume Consortia

The Terpene Consortium

Robust Summaries for Aromatic Terpene Hydrocarbons

p-Cymene CAS No. 99-87-6

FFHPVC Terpene Consortium Registration Number

Submitted to the EPA under the HPV Challenge Program by:

The Flavor and Fragrance High Production Volume Chemical Consortia

1620 I Street, NW, Suite 925

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List of Member Companies

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The Flavor and Fragrance High Production Volume Consortia

Robust Summaries for Aromatic Terpene Hydrocarbons

The evaluation of the quality of the following data uses a systematic approach described by Klimisch [Klimisch *et al*., 1996]. Based on criteria relating to international testing standards for categorizing data reliability, four reliability categories have been established. The following categories are:

- Reliability code 1. Reliable without restrictions
- Reliability code 2. Reliable with restrictions
- Reliability code 3. Not reliable
- Reliability code 4. Not assignable

1 Chemical and Physical Properties

1.1 Melting Point

Substance Name	*p*-Cymene
CAS No.	99-87-6
Method/guideline	Measured
GLP	No
Melting Point	-67.94 °C
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Merck Index (1996) 12th edition, Susan Budavari, editor, Merck & Co. Inc., Whitehouse Station, NJ.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Method/guideline	Measured
GLP	No
Melting Point	-68 °C
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	International Programme on Chemical Safety & The Commission of the European Communities (1993) *p*-Cymene. www.inchem.org.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Method/guideline	Measured
GLP	No
Melting Point	-67.9 °C
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	CRC Handbook of Chemistry and Physics (1986) 67th edition, Robert C. Weast, editor, The Chemical Rubber Co. Press, Inc. Boca Raton, Florida.

1.2 Boiling Point

Substance Name	*p*-Cymene
CAS No.	99-87-6
Method/guideline	Measured
GLP	No
Year	1997
Boiling Point	177.1 °C
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Merck Index (1996) 12th edition, Susan Budavari, editor, Merck & Co. Inc., Whitehouse Station, NJ.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Method/guideline	Measured
GLP	No
Year	1958
Boiling Point	177 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Only short abstract available.
References	Furnas D.W. and Hine, C.H. (1958) Neurotoxicity of some selected hydrocarbons. AMA Arch Ind Health, 18, 9-15.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Method/guideline	Measured
GLP	No
Boiling Point	177 °C
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.

Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	International Programme on Chemical Safety & The Commission of the European Communities (1993) p-Cymene. www.inchem.org.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Method/guideline	Measured
GLP	No
Boiling Point	176 °C
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Fragrance Materials Association (FMA) Unpublished report.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Method/guideline	Measured
GLP	No
Boiling Point	177.1 °C
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	CRC Handbook of Chemistry and Physics (1986) 67th edition, Robert C. Weast, editor, The Chemical Rubber Co Press, Inc., Boca Raton, Florida.

1.3 Vapor Pressure

Substance Name	*p*-Cymene
CAS No.	99-87-6
Method/guideline	Measured
Vapor Pressure	1.46 mm Hg (194.6 Pa)
Temperature	25 °C

Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	Mackay D. Bobra A., Chan D., and Shiu W. (1982) Vapor pressure correlations for low volatility environmental chemicals. Environ. Sci. Technology, 16**,** 645-649.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Method/guideline	Measured
GLP	No
Vapor Pressure	1.50 mm Hg (200 Pa)
Temperature	20 °C
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	International Programme on Chemical Safety & The Commission of the European Communities (1993) *p*-Cymene. www.inchem.org.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Method/guideline	Calculated/Antoine & Grain method
Vapor Pressure	1.11 mm Hg (148 Pa)
Temperature	25 °C
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	MPBPVP EPI Suite (2000) U S Environmental Protection Agency.

1.4 n-Octanol/Water Partition Coefficient

Substance Name	*p*-Cymene
CAS No.	99-87-6
Method/guideline	Measured

GLP	No
Year	1980
Log Pow	4.1
Temperature	23 +\-1.5 °C
Remarks for Test Conditions	At a temperature of 23 +\-1.5 °C, a mixture of purified octanol and water was shaken for 30 minutes and separated by centrifugation (10,000 rpm, 30 minutes). *p*-Cymene was dissolved in the water-saturated octanol and then added to a steel tube which was then sealed and the contents were equilibrated by shaking for 4-5 minute intervals, 10 minutes apart. Afterwards, the tube was centrifuged (10,000 rpm, 30 minutes) and the octanol and water layers were sampled and analyzed by GC. The octanol sample was diluted with methanol prior to analysis. The test was conducted in duplicate.
Remarks for Results	Results given as K = 1.26E4 (6% standard deviation)
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Banerjee S., Yalkowsky, S., and Valvani, S.C. (1980) Water solubility and octanol/water partition coefficients of organics. Limitations of the solubility-partition coefficient correlation. Environmental Science and Technology, 14(10), 1227-1229.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Method/guideline	Calculated
Log Pow	4.1
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	KOWWIN EPI Suite (2000) U S Environmental Protection Agency, (Hansch C. et al., 1995).

Substance Name	*p*-Cymene
CAS No.	99-87-6
Method/guideline	Calculated
Log Pow	4.19
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.

References	Interactive Analysis LogP and LogW Predictor: Database contributed by Syracuse Research Corporation, SciVision, Albany Molecular Research, Inc., eduSoft LC, Cambridge Soft. www.logp.com.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue cumene
Method/guideline	Calculated
Log Pow	3.63
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	Mackay D., Bobra, A., Shiu, W.Y., and Yalkowsky, S.H. (1980) Relationships between aqueous solubility and octanol-water partition coefficients. Chemosphere, 9(11), 701-711.

1.5 Water Solubility

Substance Name	*p*-Cymene
CAS No.	99-87-6
GLP	No
Year	1980
Value (mg/L) at Temperature	23.35 mg/L at 25 °C
Remarks for Test Conditions	Distilled water was mixed with an excess of *p*-cymene by constant or intermittent shaking in a sealed stainless steel centrifuge tube and allowed to equilibrate (usually within 1 week). Afterwards, the tube was centrifuged (10,000 ppm, 60 minutes) and water samples were taken and analyzed by GC. The test was conducted at least twice and the analysis of samples was conducted in duplicate.
Remarks for Results	Results reported as 174 uM.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Banerjee S., Yalkowsky, S., and Valvani, S.C. (1980) Water solubility and octanol/water partition coefficients of organics. Limitations of the solubility-partition coefficient correlation. Environ. Sci. Technol., 14(10), 1227-1229.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Method/guideline	Measured
GLP	No
Value (mg/L) at Temperature	20 mg/L at 25 °C
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	International Programme on Chemical Safety & The Commission of the European Communities (1993) *p*-Cymene. www.inchem.org.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue cumene
GLP	No
Year	1974
Value (mg/L) at Temperature	500 mg/L at 25 °C in synthetic seawater
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Price K.S., Waggy, G.T., and Conway, R.A. (1974) Brine shrimp bioassay and seawater BOD of petrochemicals. J Water Pollution Control Fed, 46(1), 63-77.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Method/guideline	Calculated
Value (mg/L) at Temperature	11.675 mg/L
Remarks for Results	Reported as LogW = -4.06 W = 0.000087 mol/L W = 0.011675 g/L Lipinski Number: 4
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.

References

Interactive Analysis LogP and LogW Predictor: Database contributed by Syracuse Research Corporation, SciVision, Albany Molecular Research, Inc., eduSoft LC, Cambridge Soft. www.logp.com.

2 Environmental Fate and Pathways

2.1 Photodegradation

Substance Name	*p*-Cymene
CAS No.	99-87-6
Method/guideline	Calculated
Test Type	AOPWIN
Halflife t1/2	15.03 hours
Remarks for Test Conditions	The data are obtained by a recognized SAR method and are based upon measured OH, ozone and NO3 rate constants.
Remarks for Results	Reaction with hydroxyl radicals
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
References	AOPWIN EPI Suite (2000) U S Environmental Protection Agency.

2.2 Biodegradation

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue cumene
Method	Modified standard BOD procedure (freshwater)
Test Type	Aerobic
GLP	No
Year	1974
Contact Time	20 days
Innoculum	Domestic wastewater
Remarks for Test Conditions	Domestic wastewater was filtered through glass wool and added (3 ml/bottle) to BOD bottles. Aerated dilution water was added to fill the bottles halfway. Cumene was added to provide concentrations of 3, 7, or 10 mg/L providing a potential oxygen demand of 3-30 mg/L over 20 days. A minimum of 2 concentrations was tested in duplicate. Dissolved oxygen (DO) was monitored periodically and if it dropped below 4.0 mg/L, the

	was monitored periodically and if it dropped below 4.0 mg/L, the bottle contents were re-aerated until a DO level of 7 mg/L was reached. Routine analysis for nitrates and nitrites was performed using the methods described by APHA (1971) with principal modifications as follows: sulfanilic acid was omitted from the color reagent and adjustments to the procedure to allow for smaller sample sizes. Results were recorded as "percent bio-oxidation" which was defined as the difference between the cumulative oxygen uptake for oxidation of the carbonaceous material in the test sample bottle from day 0 to the day of interest in mg/L and the cumulative oxygen uptake in a blank, containing the same amount and type of microbial seed as the test sample bottle, from day 0 to the day of interest in mg/L divided by the initial concentration of the test compound in mg/L times the theoretical oxygen demand or the weight ratio of oxygen required per mg of compound for complete conversion of the compound to CO2 and water.
Degradation % After Time	40% after 5 days; 62% after 10 days; 63% after 15 days; 70% after 20 days
Time required for 10% degradation	Less than 5 days
Remarks Results	Theoretical oxygen demand = 3.50 mg/mg; measured chemical oxygen demand = 1.13 mg/mg
Conclusion Remarks	In freshwater, cumene showed a 70% bio-oxidation within 20 days. The authors concluded that cumene was biodegradable in freshwater.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
Reference	Price K.S., Waggy, G.T., and Conway, R.A. (1974) Brine shrimp bioassay and seawater BOD of petrochemicals. J Water Pollution Control Fed, 46(1), 63-77.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue cumene
Method/guideline	Modified standard BOD procedure (synthetic seawater)
Test Type	Aerobic
GLP	No
Year	1974
Contact Time	20 days
Innoculum	Settled raw wastewater added to seawater
Remarks for Test Conditions	Wastewater was filtered through glass wool and added (3 ml/bottle) to BOD bottles. Aerated dilution water was added to fill the bottles halfway. Cumene was added to provide concentrations of 3, 7, or 10 mg/L providing a potential oxygen

	demand of 3-30 mg/L over 20 days. A minimum of 2 concentrations was tested in duplicate. Dissolved oxygen (DO) was monitored periodically and if it dropped below 4.0 mg/L, the bottle contents were re-aerated until a DO level of 7 mg/L was reached. Routine analysis for nitrates and nitrites was performed using the methods described by APHA (1971) with principal modifications as follows: sulfanilic acid was omitted from the color reagent and adjustments to the procedure to allow for smaller sample sizes. Results were recorded as "percent bio-oxidation" which was defined as the difference between the cumulative oxygen uptake for oxidation of the carbonaceous material in the test sample bottle from day 0 to the day of interest in mg/L and the cumulative oxygen uptake in a blank, containing the same amount and type of microbial seed as the test sample bottle, from day 0 to the day of interest in mg/L divided by the initial concentration of the test compound in mg/L times the theoretical oxygen demand or the weight ratio of oxygen required per mg of compound for complete conversion of the compound to CO2 and water.
Degradation % After Time	3% after 10 days; 3% after 15 days; 2% after 20 days
Results	Theoretical oxygen demand = 3.50 mg/mg; measured chemical oxygen demand = 1.13 mg/mg
Conclusion Remarks	In synthetic seawater, cumene showed a virtually no bio-oxidation (2%) after 20 days. The authors concluded that cumene showed no biodegradation in synthetic seawater.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
Reference	Price K.S., Waggy, G.T., and Conway, R.A. (1974) Brine shrimp bioassay and seawater BOD of petrochemicals. J Water Pollut Control Fed, 46(1), 63-77.

2.3 Fugacity

Substance Name	*p*-Cymene
CAS No.	99-87-6
Model Conditions	25 °C, 1,000 kg
Test Type	Environmental Equilibrium Partitioning Model
Method	Level III Fugacity Model
Model Used	EQC Model Level III, Mackay, 1996a, 1996b
Input Parameters	MW, VP, log Kow, MP, water solubility
Year	1996
Media	Air

Estimated Distribution and Media Concentration	4.73% into air
Model data and results	Mass amount, half-life and emission rate
Remarks	At emission rate of 1000 kg/hr, half -life in air is 17 hours.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated. The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism
References	Mackay D., A.DiGuardo, S.Paterson, G.Kicsi and C.E.Cowan (1996a) Assessing the fate of new and existing chemicals: a five-stage process. Environ. Toxicol. Chem. 15(9): 1618-1626. Mackay D., A.DiGuardo, S.Paterson and C.E.Cowan (1996b) Evaluating the fate of a variety of of types of chemicals using the EQC model. Environmental Toxicology and Chemistry, 15(9), 1627-1637.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Model Conditions	25 °C, 1,000 kg
Test Type	Environmental Equilibrium Partitioning Model
Method	Level III Fugacity Model
Model Used	EQC Model Level III, Mackay, 1996a, 1996b
Input Parameters	MW, VP, log Kow, MP, water solubility
Year	1996
Media	Water
Estimated Distribution and Media Concentration	27.7% into water
Model data and results	Mass amount, half-life and emission rate
Remarks	At emission rate of 1000 kg/hr, half -life in air is 360 hours.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated. The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism
References	Mackay D., A.DiGuardo, S.Paterson, G.Kicsi and C.E.Cowan (1996a) Assessing the fate of new and existing chemicals: a five-stage process. Environ. Toxicol. Chem. 15(9): 1618-1626. Mackay D., A.DiGuardo, S.Paterson and C.E.Cowan (1996b) Evaluating the fate of a variety of of types of chemicals using the EQC model. Environmental Toxicology

and Chemistry, 15(9), 1627-1637.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Model Conditions	25 °C, 1,000 kg
Test Type	Environmental Equilibrium Partitioning Model
Method	Level III Fugacity Model
Model Used	EQC Model Level III, Mackay, 1996a, 1996b
Input Parameters	MW, VP, log Kow, MP, water solubility
Year	1996
Media	Soil-Water Partition Coefficient
Estimated Distribution and Media Concentration	65.3% into soil
Model data and results	Mass amount, half-life and emission rate
Remarks	At emission rate of 1000 kg/hr, half -life in air is 360 hours.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated. The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism
References	Mackay D., A.DiGuardo, S.Paterson, G.Kicsi and C.E.Cowan (1996a) Assessing the fate of new and existing chemicals: a five-stage process. Environ. Toxicol. Chem. 15(9): 1618-1626. Mackay D., A.DiGuardo, S.Paterson and C.E.Cowan (1996b) Evaluating the fate of a variety of of types of chemicals using the EQC model. Environmental Toxicology and Chemistry, 15(9), 1627-1637.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Model Conditions	25 °C, 1,000 kg
Test Type	Environmental Equilibrium Partitioning Model
Method	Level III Fugacity Model
Model Used	EQC Model Level III, Mackay, 1996a, 1996b
Input Parameters	MW, VP, log Kow, MP, water solubility

Year	1996
Media	Sediment-Water Partition Coefficient
Estimated Distribution and Media Concentration	2.22% into sediment
Model data and results	Mass amount, half-life and emission rate
Remarks	At emission rate of 0 kg/hr, half -life in air is 1440 hours.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated. The data are obtained by a recognized fugacity calculation method. Data are considered reliable with restriction because this method does not allow for biodegradation or metabolism
References	Mackay D., A.DiGuardo, S.Paterson, G.Kicsi and C.E.Cowan (1996a) Assessing the fate of new and existing chemicals: a five-stage process. Environ. Toxicol. Chem. 15(9): 1618-1626. Mackay D., A.DiGuardo, S.Paterson and C.E.Cowan (1996b) Evaluating the fate of a variety of of types of chemicals using the EQC model. Environmental Toxicology and Chemistry, 15(9), 1627-1637.

3 Ecotoxicity

3.1 Acute Toxicity to Fish

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Minimum purity of 80%
Method/guideline	"Methods for acute toxicity tests with fish, macroinvertebrates, and amphibians" (EPA, 1975)
Test Type	Experimental
GLP	Ambiguous
Year	1981
Species/Strain/Supplier	Sheepshead minnow (*Cyprinodon variegatus*, 8-15 mm)
Exposure Period	96 hour
Analytical monitoring	Not described.
Remarks for Test Conditions	Groups of 10 sheepshead minnows were used in a 96-hour static test to evaluate the potential toxicity of p-cymene. The test vessels were either 4-L glass jars filled with 3 L of test water (filtered [5 um] natural seawater) or 19-L glass jars filled with 15 L test solution. No aeration was used. The use of a solvent for p-cymene was not described. Dissolved oxygen was measured at the beginning of the test and daily thereafter. pH was measured in the low and high concentration groups at the beginning and end of the test. Specific nominal concentrations and/or measured concentrations were not reported. LC50s at 24, 48, 72, and 96 hours were calculated with a computer program (Stephan, 1977) that determined the most appropriate statistical method (moving average angle analysis, probit analysis, or binomial probability) to apply.
Endpoint value	24 hour LC50 = 56 (32-100, 95% c.i.) ppm; 48 hour LC50 = 50 (38-68, 95% c.i.) ppm; 72 hour LC50 = 48 (36-64, 95% c.i.) ppm; 96 hour LC50 = 48 (36-64, 95% c.i.) ppm; NOEC=10 ppm
Unit	mg/L
Conclusion Remarks	The authors concluded that substances tested with a 96-hour LC50 ranging from 10-500 ppm were slightly toxic to practically non-toxic.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
Reference	Heitmuller P.T., Hollister, T.A., and Parrish, P.R. (1981). Acute toxicity of 54 industrial chemicals to sheepshead minnows (Cyprinodon variegatus). Bull Environm Contam Toxicol., 27, 596-604.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue cumene; purity of 99.4%
Method/guideline	Acute toxicity test using guidelines from 40 CFR 797.1400 (EPA, 1985; 1987)
Test Type	Experimental
GLP	Yes
Year	1995
Species/Strain/Supplier	Rainbow trout (*Oncorhynchus mykiss*, 31-46 mm)
Exposure Period	96 hour
Analytical monitoring	HPLC
Remarks for Test Conditions	Tests were conducted using a temperature-controlled water bath with a flow-through system that allowed 13 volume replacements per day. Ten organisms per test vessel were used. Six nominal test concentrations of 8.7, 13, 21, 32, 49, or 75 mg/L with a control group were run in duplicate. Filtered (0.45 um) and unfiltered water from the test vessels was sampled at the beginning, midpoint and end of each test and tested for cumene concentration. In addition, dissolved oxygen, temperature, hardness, and pH were measured daily. The photoperiod was 16:8. LC50s were calculated using a computer program (Stephan, 1983) that used mean measured concentrations and corresponding mortality data (the program used binomial interpolation, moving averages or probit depending on the data).
Nominal concentrations as mg/L	0, 8.7, 13, 21, 32, 49, or 75
Measured concentrations as mg/L	ND (less than 0.27), 0.87, 1.2, 1.9, 2.8, 4.9, or 6.4
Endpoint value	24 hour LC50 = 6.4 (5.5-9.3, 95% c.i.) mg/L; 48 hour LC50 = 5.8 (5.1-6.9, 95% c.i.) mg/L; 72 hour LC50 = 5.2 (4.5-6.2, 95% c.i.) mg/L; 96 hour LC50 = 4.8 (4.2-5.5, 95% c.i.) mg/L; NOEC = 1.9 mg/L
Unit	mg/L
Remarks fields for results	The measured concentrations were approximately 10% of the nominal concentrations. Water hardness, pH and temperature were 30-36 mg/L as CaCO3, 7.0, and 12 C, respectively.
Conclusion Remarks	The authors concluded that cumene is moderately toxic to fish but cumene's high volatility would limit its toxicological impact to an aquatic environment.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.

Reference	Glickman A.H., Alexander, H.C., Buccafusco, R.J., Morris, C.R., Francis, B.O., Surprenant, D.C., and Ward, T.J. (1995) An evaluation of the aquatic hazard of cumene (isopropyl benzene). Ecotoxicol Environ Saf., 31(3), 287-289.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue cumene
Method/guideline	OECD Guideline 203
Test Type	Experimental
GLP	Ambiguous
Year	1993
Species/Strain/Supplier	Red killifish (*Oryzias latipes*)
Exposure Period	96 hour
Remarks for Test Conditions	Groups of 10 red killifish were exposed to 5 concentrations of cumene in 2 liters of test solution at 20 °C under semi-static conditions. Specific nominal and measured concentrations were not reported. DMSO and/or dispersant (HCO-40 from Nikkou Chemicals Co.) were used if a solvent was necessary (not reported if these was necessary for cumene).
Endpoint value	96 hour LC50 = 18 mg/L
Unit	mg/L
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
Reference	Yoshioka Y., and Ose, Y. (1993) A quantitative structure-activity relationship and ecotoxicological risk quotient for the protection from chemical pollutants. Environ Toxicol Water Qual., 8, 87-101.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue cumene; purity of 99.4%
Method/guideline	Acute toxicity test using guidelines from 40 CFR 797.1400 (EPA, 1985; 1987)
Test Type	Experimental
GLP	Yes
Year	1995

Species/Strain/Supplier	Sheepshead minnow (*Cyprinodon varigatus*, 22-35 mm)
Exposure Period	96 hour
Analytical monitoring	HPLC
Remarks for Test Conditions	Tests were conducted using a temperature-controlled water bath with a flow-through system that allowed 13 volume replacements per day. Ten organisms per test vessel were used. Six nominal test concentrations of 23, 36, 55, 84, 130, or 200 mg/L with a control group were run in duplicate. Filtered (0.45 um) and unfiltered water from the test vessels was sampled at the beginning, midpoint and end of each test and tested for cumene concentration. In addition, dissolved oxygen, temperature, salinity, and pH were measured daily. The photoperiod was 16:8. LC50s were calculated using a computer program (Stephan, 1983) that used mean measured concentrations and corresponding mortality data (the program used binomial interpolation, moving averages or probit depending on the data).
Endpoint value	24 hour LC50 = 8.1 (5.6-14, 95% c.i.) mg/L; 48 hour LC50 = 5.7 (4.8-8.1, 95% c.i.) mg/L; 72 hour LC50 = 4.8 (4.5-5.2, 95% c.i.) mg/L; 96 hour LC50 = 4.7 (4.3-5.6, 95% c.i.) mg/L; NOEC = less than2.9 mg/L
Unit	mg/L
Nominal concentrations as mg/L	0, 23, 36, 55, 84, 130, or 200
Measured concentrations as mg/L	ND (less than 0.16), 2.9, 4.3, 5.6, 8.1, 14, or 17
Conclusion Remarks	The authors concluded that cumene is moderately toxic to fish but cumene's high volatility would limit its toxicological impact to an aquatic environment.
Remarks for Results	The measured concentrations were approximately 10% of the nominal concentrations. Water salinity, pH and temperature were 32 ppt, 8.0, and 25 C, respectively.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
Reference	Glickman A.H., Alexander, H.C., Buccafusco, R.J., Morris, C.R., Francis, B.O., Surprenant, D.C., and Ward, T.J. (1995) An evaluation of the aquatic hazard of cumene (isopropyl benzene). Ecotoxicol Environ Saf., 31(3), 287-289.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Method/guideline	ECOSAR
Test Type	Calculated
GLP	No

Species/Strain/Supplier	Fish
Exposure Period	14 days
Remarks for Test Conditions	Based on: Kow = 4.10, melting point = -68 °C, water solubility = 25 mg/L
Endpoint value	14 day LC50 = 2.671 mg/L (Neutral organics)
Unit	mg/L
Conclusion Remarks	The data are obtained by a recognized SAR calculation and are consistent with chemical structure.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) U.S. Environmental Protection Agency

Substance Name	*p*-Cymene
CAS No.	99-87-6
Method/guideline	ECOSAR
Test Type	Calculated
GLP	No
Species/Strain/Supplier	Fish
Exposure Period	96 hour
Remarks for Test Conditions	Based on: Kow = 4.10, melting point = -68 °C, water solubility = 25 mg/L
Endpoint value	96 hour LC50 = 1.056 mg/L (Neutral organics)
Unit	mg/L
Conclusion Remarks	The data are obtained by a recognized SAR calculation and are consistent with chemical structure.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) U.S. Environmental Protection Agency

Substance Name	*p*-Cymene
CAS No.	99-87-6
Method/guideline	ECOSAR
Test Type	Calculated

GLP	No
Species/Strain/Supplier	Fish (SW)
Exposure Period	96 hour
Remarks for Test Conditions	Based on: Kow = 4.10, melting point = -68 °C, water solubility = 25 mg/L
Endpoint value	96 hour LC50 = 0.668 mg/L (Neutral organics)
Unit	mg/L
Conclusion Remarks	The data are obtained by a recognized SAR calculation and are consistent with chemical structure.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) U.S. Environmental Protection Agency

3.2 Acute Toxicity to Aquatic Invertebrates

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Purity greater than 80%
Method/guideline	"Methods for acute toxicity tests with fish, macroinvertebrates, and amphibians" (EPA, 1975)
Test Type	Experimental
GLP	Ambiguous
Year	1980
Species/Strain/Supplier	*Daphnia magna*
Analytical procedures	Dissolved oxygen and temperature measured with a YSI Model 54BP probe, pH measured with pH meter, and total hardness determined according to APHA et al. (1975).
Test Details	24 and 48 hours
Remarks for Test Conditions	The use of a vehicle (triethylene glycol, ethanol, acetone or dimethylformamide) was dependent on the solubility of the chemical. It was not stated whether a vehicle was used for *p*-cymene. Five to 8 concentrations were tested. Within 30 minutes of solution preparation, soluble test materials were tested with 5 *daphnids* randomly placed in 3 150 ml jars containing test solution; otherwise 15 *daphnia* were placed in 2 liter jars containing test solution. In either case, the jars were covered with plastic wrap held with an elastic band. The control consisted of the same dilution water, test conditions and test

	organisms, but no test substance or vehicle. Observations were made at 24 and 48 hours. LC50s and 95% confidence limits were determined using a moving average angle method, but if the data did not meet the requirements of this method a probit analysis was used and if this did not work, a binomial probability analysis was conducted. The paper did not specify which method was used for calculating the LC50s for *p*-cymene.
EC50, EL50, LC0, at 24,48 hours	24 hour LC50 = 9.4 mg/L (7.9-11, 95% conf.int.); 48 hour LC50 = 6.5 mg/L (4.3-10, 95% conf.int.)
Unit	mg/L
Biological observations	No discernable effect at less than 4.6 mg/L. No other description given.
Remarks for Results	Results were limited to tabular reporting of LC50s. Measured dissolved oxygen concentrations ranged from 6.5-9.1 mg/L, measured pH values ranged from 6.7-8.1 and 7.4-9.4 for solutions with a hardness of 72 and 173 mg CaCO3/L, respectively.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Data Reliability Remarks	Code 2. Basic data given: comparable to guidelines/standards.
Reference	LeBlanc G.A. (1980) Acute toxicity of priority pollutants to water flea (*Daphnia magna*). Bull Environ Contam Toxicol., 24, 684-691.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue cumene; purity of 99.4%
Method/guideline	Acute toxicity test using guidelines from 40 CFR 797.1400 (EPA, 1985; 1987)
Test Type	Experimental
GLP	Yes
Year	1995
Species/Strain/Supplier	Mysid shrimp (<= 1 day)
Analytical procedures	GC Analysis
Test Details	96 hours
Remarks for Test Conditions	Tests were conducted using a temperature-controlled water bath with a flow-through system that allowed 13 volume replacements per day. Ten organisms per test vessel were used. Five nominal test concentrations of 1.8, 3.0, 4.8, 7.2, or 12.0 mg/L with a control group were run in duplicate. Filtered (0.45 um) and unfiltered water from the test vessels was sampled at the beginning, midpoint and end of each test and tested for cumene concentration. In addition, dissolved oxygen, temperature, salinity, and pH were measured daily. The photoperiod was 14:10.

	photoperiod was 14:10.
EC50, EL50, LC0, at 24,48 hours	24 hour LC50 greater than 2.0 mg/L; 48 hour LC50 = 1.6 (1.1-2.0, 95% c.i.) mg/L; 72 hour LC50 = 1.4 (1.1-2.0, 95% c.i.) mg/L; 96 hour LC50 = 1.3 (1.1-2.0, 95% c.i.) mg/L; NOEC = 0.68 mg/L
Unit	mg/L
Nominal concentrations as mg/L	0, 1.8, 3.0, 4.8, 7.2, or 12.0
Measured concentrations as mg/L	ND (less than 0.005), 0.22, 0.38, 0.68, 1.1 or 2.0
Biological observations	The water salinity, pH and temperature were 19 ppt, 7.6, and 25 C, respectively.
Appropriate statistical evaluations?	Yes. LC50s were calculated using a computer program (Stephan, 1983) that used mean measured concentrations and corresponding mortality data (program used binomial interpolation, moving averages or probit depending on the data).
Remarks for Results	The measured concentrations were approximately 10% of the nominal concentrations.
Conclusion remarks	In a series of acute tests with other aquatic species (rainbow trout, sheepshead minnow, and daphnia), mysid shrimp appeared to be the most sensitive with a NOEC of 0.68 mg/L. The authors concluded that cumene is moderately toxic to invertebrates but cumene's high volatility would limit its toxicological impact to an aquatic environment.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Data Reliability Remarks	Code 1. Guideline study.
Reference	Glickman A.H., Alexander, H.C., Buccafusco, R.J., Morris, C.R., Francis, B.O., Surprenant, D.C., and Ward, T.J. (1995) An evaluation of the aquatic hazard of cumene (isopropyl benzene). Ecotoxicol Environ Saf., 31(3), 287-289.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue cumene; purity of 99.4%
Method/guideline	Acute toxicity test using guidelines from 40 CFR 797.1400 (EPA, 1985; 1987)
Test Type	Experimental
GLP	Yes
Year	1995
Species/Strain/Supplier	*Daphnia magna* (<=1 day)
Analytical procedures	HPLC
Test Details	48 hours

Remarks for Test Conditions	Tests were conducted using a temperature-controlled water bath with a flow-through system that allowed 6 volume replacements per day. Ten organisms per test vessel were used. Five nominal test concentrations of 12, 20, 33, 55, or 91 mg/L with a control group were run in duplicate. Filtered (0.45 um) and unfiltered water from the test vessels was sampled at the beginning, midpoint and end of each test and tested for cumene concentration. In addition, dissolved oxygen, temperature, hardness, and pH were measured daily. The photoperiod was 16:8.
EC50, EL50, LC0, at 24,48 hours	24 hour LC50 = 4.8 (4.3-5.6, 95% c.i) mg/L; 48 hour LC50 = 4.0 (3.5-4.5, 95% c.i.) mg/L; NOEC = 1.5 mg/L
Unit	mg/L
Nominal concentrations as mg/L	0, 12, 20, 33, 55, or 91
Measured concentrations as mg/L	ND (less than 0.16), 1.5, 2.4, 4,0, 6.1 or 8.9
Biological observations	Water hardness, pH and temperature were 160-180 mg/L as CaCO3, 8.3, and 20 C, respectively.
Appropriate statistical evaluations?	Yes. LC50s were calculated using a computer program (Stephan, 1983) that used mean measured concentrations and corresponding mortality data (program used binomial interpolation, moving averages or probit depending on the data).
Remarks for Results	The measured concentrations were approximately 10% of the nominal concentrations.
Conclusion remarks	The authors concluded that cumene is moderately toxic to invertebrates but cumene's high volatility would limit its toxicological impact to an aquatic environment.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Data Reliability Remarks	Code 1. Guideline study.
Reference	Glickman A.H., Alexander, H.C., Buccafusco, R.J., Morris, C.R., Francis, B.O., Surprenant, D.C., and Ward, T.J. (1995) An evaluation of the aquatic hazard of cumene (isopropyl benzene). Ecotoxicol Environ Saf., 31(3), 287-289.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue cumene
Method/guideline	Toxicity screening test/Hatching procedure
Test Type	Experimental
GLP	No
Year	1974
Species/Strain/Supplier	Brine shrimp (*Artemia salina*)

Test Details	24 hours
Remarks for Test Conditions	To ensure survival of the shrimp in the test solution, a hatching procedure was used in which shrimp eggs were allowed to hatch and viable shrimp were removed with a medicine dropper. In the screening test, bottles containing 100, 1,000, or 10,000 mg cumene/L test solution were used. Brine shrimp suspension (1 ml) was added by pipette at a titer of 30-50 shrimp/ml. Bottles were loosely capped and maintained at 24.5 °C for 24 hours. A colony counter was used to determine the number of live and dead shrimp at the end of the test period. To determine the median tolerance limit, the same procedure was used with more specific concentrations. If the toxicity range in the screening test was 100-1,000 mg/L, the concentrations used were 100, 180, 320, 560, or 1,000 mg/L. The reviewer assumes these concentrations were used since the final median tolerance limit was within this range. If the toxicity range was less than 100 mg/L but greater than10 mg/L, the concentrations used were 10, 1832, 56 or 100 mg/L. The percent survival versus the test dosage concentration (log scale) was plotted. The median tolerance limit was the concentration at 50% survival when a straight line was plotted.
EC50, EL50, LC0, at 24,48 hours	24 hour median tolerance limit = 110 mg/L
Unit	mg/L
Nominal concentrations as mg/L	100, 180, 320, 560, or 1,000
Biological observations	Movement, or lack thereof, of phyllopodia (swimming appendages) was used to indicate survival (movement) or death (no movement). Clinging together of 2 or more shrimp indicated near lethal concentrations.
Remarks for Results	The reviewer assumes the concentrations of 100, 180, 320, 560, or 1,000 mg/L were used since the final median tolerance limit was within this range.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Data Reliability Remarks	Code 2. Basic data given: comparable to guidelines/standards.
Reference	Price K.S., Waggy, G.T., and Conway, R.A. (1974) Brine shrimp bioassay and seawater BOD of petrochemicals. J Water Pollut Control Fed., 46(1), 63-77.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Method/guideline	ECOSAR
Test Type	Calculated
Species/Strain/Supplier	*Daphnia magna*
Test Details	16 days

Remarks for Test Conditions	Based on: Kow = 4.10, melting point = -68 °C, water solubility = 25 mg/L
EC50, EL50, LC0, at 24,48 hours	16 day EC50 = 0.168 mg/L
Conclusion Remarks	The data are obtained by a recognized SAR calculation and are consistent with chemical structure.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Data Reliability Remarks	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) U.S. Environmental Protection Agency.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Method/guideline	ECOSAR
Test Type	Calculated
Species/Strain/Supplier	Mysid shrimp
Test Details	96 hours
Remarks for Test Conditions	Neutral organics, based on Kow = 4.10, melting point = -68 °C C, water solubility = 25 mg/L
EC50, EL50, LC0, at 24,48 hours	96 hour LC50 = 0.068 mg/L
Conclusion Remarks	The data are obtained by a recognized SAR calculation and are consistent with chemical structure.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Data Reliability Remarks	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) U.S. Environmental Protection Agency.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Method/guideline	ECOSAR
Test Type	Calculated
Species/Strain/Supplier	Daphnia magna
Test Details	48 hours
Remarks for Test Conditions	Based on: Kow = 4.10, melting point = -68 °C, water solubility = 25 mg/L
EC50, EL50, LC0, at 24,48 hours	48 hour LC50 = 1.309 mg/L
Conclusion Remarks	The data are obtained by a recognized SAR calculation and are consistent with chemical structure.

Data Qualities Reliabilities	Reliability code 4. Not assignable.
Data Reliability Remarks	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) U.S. Environmental Protection Agency.

3.3 Acute Toxicity to Aquatic Plants

Substance Name	*p*-Cymene
CAS No.	99-87-6
Method/guideline	ECOSAR
Test Type	Calculated
Species/Strain/Supplier	Green algae
Exposure Period	96 hours
Remarks for Test Conditions	Based on: Kow = 4.10, melting point = -68 °C, water solubility = 25 mg/L
Endpoint value	96 hour EC50 = 0.923 mg/L
Conclusion Remarks	The data are obtained by a recognized SAR calculation and are consistent with chemical structure.
Data Qualities Reliabilities	Reliability code 4. Not assignable.
Remarks for Data Reliability	Code 4. Calculated.
Reference	ECOSAR EPI Suite (2000) U.S. Environmental Protection Agency.

4 Human Health Toxicity

4.1 Acute Toxicity

Substance Name	*p*-Cymene
CAS No.	99-87-6
Method/guideline	Deichmann and LeBlanc, 1943
Test Type	Acute oral LD50
GLP	No
Year	1961
Species/strain	Rat
Sex	Male and Female
# of animals per sex per dose	1-3 rats/dose
Vehicle	None
Route of Administration	Oral-Gavage
Remarks for Test Conditions	Groups of rats were gavaged with 620, 940, 1400, 2100, 3200, 4700, 7100, or 10700 mg/kg bw and studied for clinical signs and mortality. Surviving animals were killed at 2 weeks. Necropsies were conducted on all rats.
Value LD50 or LC50 with confidence limits	3200 mg/kg bw
Number of deaths at each dose level	At doses of 620 to 2100 mg/kg bw, all rats survived. At 3200, 4700, 7100, and 10700 mg/kg bw, 1/2, 2/2, 3/3, and 1/1 rats died, respectively.
Remarks for Results	Prior to death, rats showed typical signs of intoxication: depression, tremor, lethargy, and muscular weakness. Necropsy was reported to show hyperemic lungs with scattered areas of hemorrhage, atelectasis and emphysema, partially digested blood and food in the stomach, petechial hemorrhages in the glandular stomach with hyperemic mucosa, bloody mucus in the upper small intestine and clear mucus in the lower small intestine, pale and mottled liver, congested liver, and distended urinary bladder. Some animals had blood-tinged urine or contained "suspended dark solid material resembling precipitated hemoglobin".
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	MacDonald W.E. (1961) Report on the determination of the approximate lethal oral dose in the rat of compounds submitted by the Hercules Powder Co. Unpublished report.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Method/guideline	Litchfield and Wilcoxon, 1949
Test Type	Acute oral toxicity
GLP	No
Year	1964
Species/strain	Rat/Osborne-Mendel
Sex	Male and Female
# of animals per sex per dose	10
Vehicle	None
Route of Administration	Oral
Remarks for Test Conditions	Groups of 10 male and 10 female Osborne-Mendel rats were orally administered *p*-cymene at various doses (not specified) to calculate an oral LD50. Rats were monitored for up to 2 weeks.
Value LD50 or LC50 with confidence limits	LD50 = 4750 mg/kg bw (95% confidence limits: 3720-6060)
Remarks for Results	Rats showed depression shortly following dosing and also coma, bloody lacrimation, diarrhea with irritable, scrawny appearance during the observation period. The LD50 was calculated to be 4750 mg/kg bw with a slope function of 1.7.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Jenner P.M., Hagan, E.C., Taylor, J.M., Cook, E.L., and Fitzhugh, O.G. (1964) Food flavourings and compounds of related structure. I. Acute oral toxicity. Fd Cosmet Toxicol 2:327-343.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue cumene
Method/guideline	Thompson
Test Type	Acute oral LD50
GLP	No
Year	1951

Species/strain	Rat
Sex	Not reported
Route of Administration	Oral
Value LD50 or LC50 with confidence limits	2910 mg/kg bw (95% C.I., 2550-3320 mg/kg bw)
Remarks for Results	The limits (+\- 1.96 standard deviations: approx. 95% Confidence Interval) were calculated by the method of Thompson. The LD50 was calculated after 14 days.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Comparable to guideline study with acceptable restrictions. One of a series of range-finding studies.
References	Smyth H.F., Jr., Carpenter, C.P., and Weil, C.S. (1951) Range-finding toxicity data: List IV. Arch Ind Hyg Occup. Med., 4, 119-122.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue cumene; purity greater than 98%
Method/guideline	Single-dose toxicity
Test Type	Acute oral/gavage
GLP	No
Year	1956
Species/strain	Rat/Wistar
Sex	Not reported
# of animals per sex per dose	20
Vehicle	Olive oil emulsified with gum arabic
Route of Administration	Oral-Gavage
Remarks for Test Conditions	Groups of Wistar rats were gavaged with cumene (specific doses not reported) to determine an oral LD50. After dosing rats were observed for up to 2 weeks.
Value LD50 or LC50 with confidence limits	1400 mg/kg bw
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Wolf M.A., Rowe, V.K., McCollister, D.D., Hollingsworth, R.L., and Oyen, F. (1956) Toxicological studies of certain alkylated benzenes and benzene. AMA Arch Ind Health, 14, 387-398.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue cumene
Method/guideline	Thompson
Test Type	Acute dermal toxicity
GLP	No
Year	1951
Species/strain	Rabbit
Sex	Not reported
Route of Administration	Dermal
Remarks for Test Conditions	The limits (+\- 1.96 standard deviations: approximately 95% confidence interval) were calculated by the method of Thompson. The LD50 was calculated after 14 days.
Value LD50 or LC50 with confidence limits	LD50 = 12.3 ml/kg bw (95% C.I. 7.69-19.7 ml/kg bw) or LD50 = 10,545 mg/kg bw
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Comparable to guideline study with acceptable restrictions. One of a series of range-finding studies.
References	Smyth H.F., Jr., Carpenter, C.P., and Weil, C.S. (1951) Range-finding toxicity data: List IV. Arch Ind Hyg Occup Med., 4, 119-122.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue cumene; purity greater than 99.94%
Test Type	Single-exposure neurobehavioral test
GLP	Ambiguous
Year	1995
Species/strain	Rat/Fischer 344/NHSD
Sex	Male and Female
# of animals per sex per dose	10
Vehicle	None
Route of Administration	Inhalation
Remarks for Test Conditions	Groups of 10 male and 10 female rats underwent a single exposure to atmospheres containing 0, 100, 500, or 1200 ppm cumene for 6 hours. Body weights were measured prior to

	cumene for 6 hours. Body weights were measured prior to exposure and at 1, 6, and 24 hours post exposure. A functional observational battery was also conducted at these times.
Remarks for Results	No effects were reported at 100 ppm in both groups of male and female rats. Cumene exposure was reported to produce alterations in the functional observational battery 1 hour post-exposure including increased incidence and severity of gait abnormalities in high-dose males, increased horizontal activity in both male and female high-dose rats and in female rats exposed to 500 ppm cumene, and decreased rectal temperature of high-dose rats of both sexes. At 6 hours post-exposure, alterations were limited to decreased toe pinch withdrawal reflexes in males rats exposed to 500 or 1200 ppm cumene. At 24 hours post-exposure, no significant differences in the functional observational battery were observed. Body weights were not affected by cumene exposure.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Data Reliabilities Remarks	Code 2. Acceptable, well-documented.
References	Cushman J.R., Norris, J.C., Dodd, D.E., Darmer, K.I., Morris, C.R. (1995) Subchronic inhalation toxicity and neurotoxicity assessment of cumene in Fischer 344 rats. J Am Coll Toxicol., 14(2), 129-147.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Test Type	Acute dermal LD50
GLP	No
Year	1973
Species/strain	Rabbit
Sex	Not reported
# of animals per sex per dose	10
Route of Administration	Dermal
Remarks for Test Conditions	Ten rabbits were dermally treated with 5000 mg/kg bw and observed for 14 days.
Value LD50 or LC50 with confidence limits	Greater than 5000 mg/kg bw
Number of deaths at each dose level	0
Remarks for Results	No rabbits died. Skin irritation was graded as follows: slight redness (3/10), moderate redness (7/10), slight edema (3/10), and moderate edema (7/10).
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.

References	Moreno O.M. (1973) Acute dermal toxicity in rabbits. *p*-Cymene. Unpublished report.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Test Type	Acute dermal
GLP	No
Year	1962
Species/strain	Rabbit/Albino
Sex	Not reported
# of animals per sex per dose	1
Route of Administration	Dermal
Vehicle	None
Value LD50 or LC50 with confidence limits	LD50 greater than 6 ml/kg bw or greater than 5144 mg/kg bw
Remarks for test conditions	Undiluted *p*-cymene was applied to the shaven abdominal skin (10 x 15 cm area) of an albino rabbit. *p*-Cymene was applied in 1 ml doses every hour for a total of 6 ml over a 6-hour exposure period. The rabbit was observed for 1 month following treatment.
Remarks for Results	Slight hyperemia of the skin was observed after 1 hour and persisted approximately 4 hours after which a slight subcutaneous edema developed. After the exposure period, the skin still was slightly edematous and over the next 5 days, it was slightly thickened, hyperemic and showed fine cracks. After the first week, the skin began to return to normal and within the month is was normal with hair growth.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	MacDonald W.E. (1962a) Acute effects of Hercules compounds applied to the skin of the rabbit. Unpublished report.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Test Type	Inhalation toxicity
GLP	No
Year	1962
Species/strain	Guinea pig

Sex	Not reported
# of animals per sex per dose	2
Route of Administration	Inhalation
Remarks for Test Conditions	Guinea pigs were exposed to atmospheres saturated with 9.7 mg p-cymene/l for a period of 5 hours. Clinical signs and mortality were recorded. Surviving animals were removed from the exposure chamber and observed for an additional week. A "lethal concentration time value (LCt)" was calculated based on the "shortest period of exposure causing death", where the concentration was expressed as mg/l and time as min.
Number of deaths at each dose level	0/2
Remarks for results	Signs reported during the first 30 minutes were those typical of irritation: excitement, pawing at the eyes and nose, increased blinking, squinting, and eye closure. Approximately 90 minutes following exposure, 1 guinea pig had a 10-15-second violent clonic convulsion followed by prolonged quivering. Afterwards, this guinea pig continued to exhibit clonic convulsions of varying degrees. The second guinea pig began quivering at about 120 minutes into the exposure and had a clonic convulsion about 30 minutes later. By the end of the exposure period, both guinea pigs were comatose and had continuous clonic convulsions. The morning after the exposure, the guinea pigs appeared fully recovered.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	MacDonald W.E. (1962b) Report on the effects in laboratory animals exposed for five hours to air saturated with the vapors of compounds submitted by the Hercules Powder Company. Unpublished report.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Test Type	Inhalation toxicity
GLP	No
Year	1962
Species/strain	Rat
Sex	Not reported
# of animals per sex per dose	3
Route of Administration	Inhalation
Remarks for Test Conditions	Rats were exposed to atmospheres saturated with 9.7 mg /L of *p*-cymene for a period of 5 hours. Clinical signs and mortality were recorded. Surviving animals were removed from the

	were recorded. Surviving animals were removed from the exposure chamber and observed for an additional week. A "lethal concentration time value (LCt)" was calculated based on the "shortest period of exposure causing death", where the concentration was expressed as mg/l and time as minutes.
Number of deaths at each dose level	0/3
Remarks for results	Signs reported during the first 30 minutes were those typical of irritation: excitement, pawing at the eyes and nose, increased blinking, squinting, and eye closure. After 45 minutes, equilibrium loss and increased salivation were noted. One-half hour later, fine tremors began and increased to quivering after another 15 minutes. Clonic convulsions were reported after another 15 minutes and the rats staggered about aimlessly until the end of the exposure. The morning after exposure, the rats appeared fully recovered.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Data Reliabilities Remarks	Code 2. Basic data given: comparable to guidelines/standards.
References	MacDonald, W.E. (1962b) Report on the effects in laboratory animals exposed for five hours to air saturated with the vapors of compounds submitted by the Hercules Powder Company. Unpublished report.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Test Type	Inhalation toxicity
GLP	No
Year	1962
Species/strain	Mouse
Sex	Not reported
# of animals per sex per dose	3
Route of Administration	Inhalation
Remarks for Test Conditions	Mice were exposed to atmospheres saturated with 9.7 mg /L of *p*-cymene for a period of 5 hours. Clinical signs and mortality were recorded. Surviving animals were removed from the exposure chamber and observed for an additional week. A "lethal concentration time value (LCt)" was calculated based on the "shortest period of exposure causing death", where the concentration was expressed as mg/l and time as min.
Value LD50 or LC50 with confidence limits	LCt = 2270 mg x min/L for 3.9 hour exposure.
Number of deaths at each dose level	3/3
Remarks for Results	Signs reported during the first 30 minutes were those typical of irritation: excitement, pawing at the eyes and nose, increased blinking, squinting, and eye closure. In addition, mice exhibited

	blinking, squinting, and eye closure. In addition, mice exhibited equilibrium loss and clonic convulsions with intervals of coma. One mouse died after 3.9 hours and another died after 4.8 hours. The 3rd mouse was comatose at termination of exposure and died during the night. Necropsies showed hyperemic lungs, mottled liver, and pale kidneys. In addition, it appeared that the heart had stopped in systole. No effects were reported in rats and guinea pigs at the same atmospheric concentration.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	MacDonald W.E. (1962b) Report on the effects in laboratory animals exposed for five hours to air saturated with the vapors of compounds submitted by the Hercules Powder Company. Unpublished report.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue cumene
Test Type	Inhalation toxicity
GLP	No
Year	1951
Species/strain	Rat
Sex	Not reported
# of animals per sex per dose	6
Route of Administration	Inhalation
Remarks for Test Conditions	Rats were exposed to atmospheres containing 8000 ppm cumene for 4 hours. Mortality over 14 days was reported.
Number of deaths at each dose level	4/6
Remarks for Results	Four out of 6 rats were reported to have died within the 14-day period. Atmospheric concentration (8000 mg/L) greater than measured saturation value of 9.7 mg/L.
Data Qualities Reliabilities	Reliability code 3. Not reliable.
Remarks for Data Reliability	Does not meet important criteria of current standard methods.
References	Smyth H.F., Jr., Carpenter, C.P., and Weil, C.S. (1951) Range-finding toxicity data: List IV. Arch Ind Hyg Occup Med., 4, 119-122.

Substance Name	*p*-Cymene

CAS No.	99-87-6
Test Type	Acute inhalation toxicity
GLP	No
Year	1958
Species/strain	Rat/Long Evans
Sex	Male
# of animals per sex per dose	8
Route of Administration	Inhalation
Remarks for Test Conditions	Groups of 8 male Long Evans rats were exposed to atmospheres containing 5000 to 10,000 ppm cumene for 4 exposures of 30, 20, 45, and 50 minutes duration. Twenty-four hours after exposure, the rats were killed and the brain, spinal cord and 1 sciatic nerve were removed and placed in 10% formalin.
Number of deaths at each dose level	5 out of 8 rats died. No further information was reported.
Remarks for Results	Cumene exposure resulted in local irritation, depression, and quivering or twitching. At necropsy, no gross or microscopic effects were reported other than those associated with respiratory irritation. Note: Exposure levels exceeded measured saturation levels of 9.7 mg/L. Therefore animals were exposed to liquid p-cymene suspended in test atmosphere
Data Qualities Reliabilities	Reliability code 3. Not reliable.
Remarks for Data Reliability	Does not meet important criteria of current standard methods.
References	Furnas D.W., and Hine, C.H. (1958) Neurotoxicity of some selected hydrocarbons. AMA Arch Ind Health,18, 9-15.

4.2 Genetic Toxicity

4.2.1 In vitro Genotoxicity

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue, cumene
Method/guideline	Preincubation Ames assay (Haworth et al., 1983)
Test Type	Ames reverse mutation
System of Testing	Bacterial
GLP	Ambiguous

Year	Undated
Species/Strain	*Salmonella typhimurium* strains TA97, TA98, TA100, and TA1535
Metabolic Activation	S9 from Aroclor 1254-induced Sprague-Dawley rat or Syrian hamster
Doses/Concentration	TA97 & TA1535: 1, 3, 10, 33, 100, or 166 ug/plate; TA100 & TA98: 1, 3, 10, 33, 100, 166, or 333 ug/plate
Statistical Methods	Positive response defined as: a reproducible, dose related increase in histidine-independent (revertant) colonies".
Remarks for Test Conditions	*Salmonella typhimurium* strains TA1535 and TA97 were incubated with up to 166 ug cumene/plate using the standard preincubation Ames assay. Similarly, *Salmonella typhimurium* strains TA100 and TA98 were incubated with up to 333 ug cumene/plate. Each cumene concentration in each strain was tested with and without metabolic activation consisting of 10 or 30% S9 from hamster liver homogenate or 10 or 30% S9 from rat liver homogenate.
Results	Cumene did not increase the number of revertants in any of the strains tested.
Cytotoxic concentration	Not given
Genotoxic Effects	None
Conclusion Remarks	Cumene had no mutagenic activity in this assay.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	NTP unpublished results (e). *Salmonella* Testing Results. Cumene. Cellular and Genetic Toxicology Branch, National Toxicology Program.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue, cumene
Method/guideline	Ames preincubation assay (Yahagi et al., 1975)
Test Type	Ames reverse mutation
System of Testing	Bacterial
GLP	Yes
Year	1987
Species/Strain	*Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537
Metabolic Activation	S9 from Aroclor 1254-induced male Sprague-Dawley rat (10% homogenate/ml)
Doses/Concentration	33, 67, 100, 333, 667, 1,000, or 2,000 ug/plate

Remarks for Test Conditions	Cumene, at concentrations of 33, 67, 100, 333, 667, 1,000, or 2,000 ug/plate, was tested in the Ames preincubation assay using *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 both with and without metabolic activation. Pluronic F127 was used to emulsify cumene. The test was also run with cumene in water rather than F127. Positive controls used were 2 ug 2-aminoanthracen, 5 ug 2-nitrofluorene, 2.5 ug sodium azide, and 75 ug 9-aminoacridine. The study was conducted in duplicate.
Results	Cumene did not affect the number of revertants in any of the strains tested. Cumene showed signs of cytotoxicity (reduced background) at 2,000 ug/plate.
Cytotoxic concentration	2,000 ug/plate
Genotoxic Effects	None
Conclusion Remarks	Cumene showed no mutagenic activity when tested in *Salmonella typhimurium* strains TA98, TA100, TA1535 and TA1537.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	Lawlor T.E., and Wagner, V.O. (1987) *Salmonella*/mammalian-microsome preincubation mutagenicity assay (Ames test). Test article: Cumene. Final Report. Microbiological Associates, Inc. Report No. T4786.502009.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue, cumene
Method/guideline	HGPRT assay
Test Type	Mutation
System of Testing	Non bacterial
GLP	Yes
Year	1985
Species/Strain	Chinese hamster ovary cells (K-1)
Metabolic Activation	Liver enzymes from Aroclor 1254-induced rats (S9)
Doses/Concentration	Trial 1:8, 16, 32, 64, 128, 150, or 175 ug/ml Trial 2: 150 or 175 ug/ml
Remarks for Test Conditions	Cultured Chinese hamster ovary cells were exposed to 8, 16, 32, 64, 128, 150, or 175 ug cumene/ml for 5 hours with and without metabolic activation (S9). Cumene was emulsified with Pluronic F127 for a final concentration of 0.04-0.05% Pluronic F127. Each treatment group consisted of 3 flasks. After the 5-hour exposure, 200 cells from each group were plated (4 plates/group), incubated, fixed and stained. In addition, 10E5-10E6 cells were seeded to larger plates on day 3. This process

	10E6 cells were seeded to larger plates on day 3. This process was repeated 3 times with the last on day 10. On day 10, 200 cells were seeded to 4 viability plates/group and 2x10E5 cells/group were plated for the mutagenicity test. The plates were incubated to day 17, fixed and stained. Ethyl methanesulfonate was used as a positive control at 100 ug/ml. Benzo(a)pyrene was used to test the enzyme system. Negative controls were untreated cells and cells exposed to the emulsifier (F127) with or without metabolic activation. Cells were counted with a Coulter Model ZB cell counter and colonies were counted either visually or with an Artek Model 981 colony counter. Results were considered positive if there was a significant (p less than 0.05) increase in mutant colonies and the response was dose related. If only one of the above criteria were met the results were considered equivocal. A second trial was conducted with S9 at 150 or 175 ug cumene/ml.
Results	In cultures without S9, the number of mutants/10E6 clonable cells for untreated control (medium), F127, 8, 16, 32, 64, and 128 ug cumene/ml, and ethyl methanesulfonate were (standard deviation in brackets) 14.8 (9.1), 4.4 (6.2), 3.0 (2.6), 12.2 (11.5), 14.0 (12.2), 5.7 (5.6), 0, and 140.5 (14.3). In activated cultures the number of mutants/10E6 clonable cells for untreated controls (medium), F127, 64, 128, 150, and 175 ug cumene/ml, and benzo(a)pyrene were (standard deviation in brackets) 12.9 (8.1), 24.9 (8.9), 2.1 (3.6), 7.5 (10.4), 4.1 (7.0), 266.8 (457.8), and 48.0 (31.4), respectively. The result for 175 ug/ml was high due to a single outlier value in the group; hence, a second trial was conducted. Mutant frequencies appeared to be high in the medium and Pluronic F127 control groups. There was no statistically significant increase in the number of mutants or a dose-response effect. Cumene was cytotoxic at concentrations of 128 ug/ml and higher. In the second trial using concentrations of 150 and 175 ug/ml, the increase in the number of mutants seen at 175 ug/ml was not repeated. In the 1st trial, cloning efficiency was significantly decreased only in activated cultures at concentrations of 128 ug/ml and higher. Cloning efficiency was not affected in non-activated cultures.
Cytotoxic concentration	128 ug/ml
Genotoxic Effects	None.
Appropriate statistical evaluations?	2-tailed t-test using MUTANT program
Conclusion Remarks	Cumene did not increase mutations in the CHO/HGPRT test with or without metabolic activation.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	Papciak R.J. (1985) CHO/HGPRT test of cumene. Project #84-2128. Gulf Life Sciences Center. Pittsburgh, PA. Unpublished report.

Substance Name	*p*-Cymene

CAS No.	99-87-6
Remarks for Substance	Data for homologue, cumene
Method/guideline	HGPRT assay
Test Type	Mutation
System of Testing	Non bacterial
GLP	Yes
Year	1987
Species/Strain	Chinese hamster ovary cells (K-1)
Metabolic Activation	Liver enzymes from Aroclor 1254-induced rats (S9)
Doses/Concentration	100, 125, 150, 175, 200, or 225 ug/ml
Remarks for Test Conditions	In preliminary toxicity tests, cultured Chinese hamster ovary cells were exposed to up to 225 ug/ml of cumene for 5 or 18 hours with and without metabolic activation (S9). In the main study, cultured Chinese hamster ovary cells were exposed to 100, 125, 150, 175, 200, or 225 ug/ml of cumene for 18 hours without S9 or for 5 hours with S9. Cumene was emulsified with Pluronic F127. Ethyl methanesulfonate was used as a positive control at 0.2 ul/ml. Benzo(a)pyrene (4 ug/ml) was used to test the enzyme system. Negative and solvent controls were untreated cells and cells exposed to the emulsifier (F127) with or without metabolic activation. Each treatment was conducted in duplicate or triplicate and colonies were counted. Results were considered positive if there was a dose-dependent increase in mutant frequency in one of the 5 tested concentrations which is at least twice that of the solvent control and untreated control, and is also increased above that of the solvent and untreated control by at least 8.7 mutants/10E6 clonable cells. If only one of the above criteria were met the results were considered equivocal.
Results	In cultures without S9, the number of mutants/10E6 clonable cells for untreated control (medium), F127, 100, and 125 ug/ml of cumene, ethyl methanesulfonate with F127, and ethyl methanesulfonate were less than 1.1 and 2.0; 4.3 and 7.1; 14.9 and 3.4; 5.4 and less than 1.1; 537.5 and 490.2; and 784.1 and 595.0. Cultures treated with 150 ug/ml and higher were too toxic to count. In activated cultures the number of mutants/10E6 clonable cells for untreated controls (medium), F127, 100, 125, and 225 ug/ml of cumene, benzo(a)pyrene with F127, and benzo(a)pyrene were 15.5 and 4.8; 1.7 and 6.8; 19.6 and 3.5; 12.9 and 2.3; 27.6 and 10.1; 350.0 and 323.7; and 347.6 and 326.4. Cultures treated with 150-200 ug/ml were too toxic to count. There was no significant increase in the number of mutants or a dose-response effect. Cumene was cytotoxic at concentrations of 150 ug/ml and higher.
Cytotoxic concentration	150 ug/ml

Genotoxic Effects	None
Remarks for Results	The authors noted that the variability shown in cytotoxicity and mutation frequencies was a result of difficulty in handling cumene, suspending it in F127, and delivering small quantities into the test medium. However, the study was considered valid since it met the validation criteria: cloning efficiency of solvent and untreated controls was greater than 50%; spontaneous mutant frequency of solvent and untreated controls is between 0 and 20 mutants per 10E6 clonable cells; and the positive control must induce a mutant frequency of at least 3 times that of the solvent control.
Conclusion Remarks	Cumene did not increase mutations in the CHO/HGPRT test with or without metabolic activation.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	Yang L.L. (1987) CHO/HGPRT Mutation Assay. Cumene. Internal Report dated June 1, 1987. #T4786.332010. Microbiological Associates Inc. Unpublished report.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Method/guideline	Paper disk method (Lyer and Szybalski, 1958)
Test Type	Reverse mutation
System of Testing	Bacterial
GLP	No
Year	1958
Species/Strain	*Escherichia coli* strain Sd-4-73
Metabolic Activation	No
Doses/ Concentration	Not reported
Remarks for Test Conditions	*E. coli* was cultured overnight at 36 C in an aerated nutrient broth containing 20 ug/ml streptomycin. Plates were prepared and *p*-cymene was added by applying to a paper disk (0.01-0.025 ml or small crystal), which was then placed on the agar. Relative mutagenicity, defined as “an approximate ratio of the number of colonies on the plate containing the mutagen to the number of colonies on the control plate, was calculated. Potent mutagens had relative mutagenicities of greater than 3 and weak and doubtful mutagens had relative mutagenicities between 1.5 and 3.
Results	*p*-Cymene produced no increase in the frequency of reversion from streptomycin dependence to independence in Sd-4-73 *E. coli.*
Genotoxic Effects	None

Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Szybalski W. (1958) Special microbiological systems. II. Observations on chemical mutagenesis in microorganisms. Annals of New York Academy of Sciences. Pp 475-489.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue, cumene, 99.7% pure
Test Type	Chromosomal aberration test
GLP	Yes
Year	1987
Species/Strain	Chinese hamster ovary cells
Metabolic Activation	Aroclor 1254 induced Sprague-Dawley rat liver microsomes
Doses/Concentration	0, 19, 31, 49, 78, 125, or 200 ug/ml without S-9 activation and 0, 24, 38, 61, 98, 156, or 225 with activation
Statistical Methods	Student's t test (p less than or = 0.05)
Remarks for Test Conditions	The test article was tested for effects on cell cycle. Duplicate cultures were treated with the culture medium (negative control), the test article alone and three concentrations of the positive control article (triethylenemelamine and cyclophosphoramide) with and without activation. One culture was harvested at first metaphase division for evaluation of chromosomal aberrations. CHO cells were seeded at 5x10-5 cells/25 cm2 flasks and incubated at 37 C for 14-16 hours. Flasks were then treated with 5 ml of test article. After exposure of 8 or 14 hours and two hours prior to harvest, the treatment medium was removed and cells were washed with PBS and refed with growth medium containing 0.1 ug/ml of colcemid. In the S-9 activated experiment, cells were exposed for 2 hours. Again, cells were separated, washed, refed, and treated with colcemid. Two hours after addition of colcemid, cells were collected and fixed. Fifty metaphase cells were scored in each duplicate flask. Cells were evaluated for a range of chromosomal changes. The second culture was treated with 0.01 mM BrdU two hours after initiation and cells were harvested 24-26 hors later for evaluation of cell cycle.
Results	Toxicity was reported at the highest dose tested with or without S-9 activation. A statistically significant increase in chromosomal aberration was reported at 156 ug/ml in the presence of S-9 compared to the vehicle control. No statistically significant increase was observed when compared to untreated control cells. The increase was within the historical control range for the contract laboratory. The authors concluded that the increase was due to low vehicle control values

Cytotoxic concentration	200 ug/ml
Genotoxic Effects	None
Appropriate statistical evaluations?	Yes
Conclusion Remarks	Cumene did not induces structural or numerical chromosomal aberrations in Chinese hamster ovary cells with or without S-9 activation
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Guideline study.
References	Putnam D.L. (1987) Chromosome aberrations in Chinese hamster ovary cells. Laboratory Study No. T4786.337012. Unpublished report.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue, cumene
Test Type	DNA Repair assay
System of Testing	Non bacterial
GLP	Yes
Year	1984
Species/Strain	F344 rat hepatocyte
Doses/Concentration	8, 16, 32, 64, 128, 256, 512, 1024, 2048, or 5,000 ug/ml
Remarks for Test Conditions	Cultured rat hepatocytes were treated with 8, 16, 32, 64, 128, 256, 512, 1024, 2048, or 5,000 ug/ml of cumene in triplicate. Nuclear grain counts (a count of 6 or more over the negative controls was considered positive) and the percentage of repair-positive cells was determined. Negative controls of medium and a 10% solution of Pluronic F68 (emulsifier) were used. 2-Acetylaminofluorene (AAF) was used as a positive control.
Results	Cytotoxicity occurred at 128 ug/ml and no nuclear grain counts were made. The percent of cells in repair (average of 3 slides) for medium, F68, AAF, 8, 16, 32, and 64 ug/ml of cumene was, respectively, 15.3, 15.3, 94.0, 12.0, 28.7, 40.0, and 16.0. The average net nuclear grain counts per slide for medium, F68, AAF, 8, 16, 32, and 64 ug cumene/ml was, respectively for slide 1: -0.87, -2.18, 71.98, -3.66, 6.48, -1.57, and -2.90; for slide 2: -2.05, -1.50, 37.69, -0.25, 0.16, 8.44, and 2.21; and for slide 3: -2.11, -0.91, 56.54, -2.67, -1.29, 2.18, and -1.98.
Cytotoxic concentration	128 ug/ml
Genotoxic Effects	Unscheduled DNA synthesis was reported at 16 ug/ml.
Remarks for Results	The results between triplicates were highly variable and inconsistent. In an independent review by Malansky (1986), it was stated that although the laboratory performing the study

	was stated that although the laboratory performing the study noted a dose-response particularly at 16 and 32 ug/ml, the data were too inconsistent to form any conclusions.
Conclusion Remarks	The independent review by Malansky (1986) suggested that this assay should be repeated at concentrations between 16 and 32 ug/ml to define a possible dose-response.
Data Qualities Reliabilities	Reliability code 3. Not reliable.
Remarks for Data Reliability	Code 3. Documentation insufficient for assessment.
References	Brecher S. (1984b) Hepatocyte primary culture/DNA repair test of cumene. Project #84-2130. Gulf Life Sciences Center, Pittsburgh, PA. Unpublished report.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue, cumene
Test Type	Cell transformation assay
System of Testing	Non bacterial
GLP	Yes
Year	1984
Species/Strain	BALB/3T3-A31-1-1 mouse fibroblasts
Doses/Concentration	5, 20, 60, or 90 ug/ml
Remarks for Test Conditions	Cultured mouse fibroblasts were treated with 5, 20, 60, or 90 ug cumene/ml. Cumene was emulsified with Pluronic F68 resulting in a final exposure to treated cultures of 0.04% Pluronic F68. Each treatment group consisted of 15 cultures for transformation and 2 cultures for colony formation. Negative controls consisted of untreated cultures and cultures treated with F68. The positive control was 1 ug 3-methylcholanthrene/ml. Focus and colony counts were done visually. Foci type was determined microscopically. The number of colonies per vessel and average number for each group were determined. Also, for each group, the colony forming efficiency was calculated. The criteria were as follows: a test was considered positive if there were "1) A two-fold increase in Type-III foci at the highest dose above that seen in negative control cultures, with or without a dose-related response or 2) a two-fold increase at two or more consecutive dose levels. Where negative control cultures have no Type-III foci, at least 2 foci would be needed for a dose level to be considered positive." Results were equivocal if the two-fold increase at a level other than the highest tested.
Results	Cytotoxicity was initially reported at 60 ug/ml as indicated by colony forming efficiency. At 90 ug/ml, cumene was very cytotoxic (no attached cells). Colony forming efficiencies for untreated controls; F68, positive controls, 5, 20, and 60 ug

	cumene/ml were, respectively, 59.5, 50, 4.5, 69, 61.5 and 22.0%. At 60 ug/ml, a 2-fold increase was reported in one of the duplicate cultures (6 type-III foci) and in the other duplicate, findings identical to that of the vehicle control were reported (2 type-II foci). No positive findings were reported at the lower concentrations.
Cytotoxic concentration	60 ug/ml
Genotoxic Effects	Apparent positive finding at 60 ug/ml.
Remarks for Results	The authors of the report indicate that toxicity was seen at 60 ug/ml yet report a 2-fold increase in one of the duplicates as a positive finding.
Conclusion remarks	Considering that toxicity was reported and that the 2-fold increase only occurred in one duplicate, the results, at best, could be considered equivocal.
Data Qualities Reliabilities	Reliability code 3. Not reliable.
Remarks for Data Reliability	Code 3. Relevant methodological deficiencies.
References	Brecher S. (1984a) Cell transformation test of cumene. Project #84-2131. Gulf Life Sciences Center. Pittsburgh, PA. Unpublished report.

4.2.2 In vivo Genotoxicity

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue cumene
Method/guideline	Micronucleus assay
Test Type	Clastogenic study
GLP	Yes
Year	1984
Species/Strain	Crl:CDR-1 (ICR) BR Swiss mouse
Sex	Male and Female
Route of Administration	Oral-Gavage
Doses/Concentration	250, 500 or 1000 mg/kg bw/day
Exposure Period	2 days
Remarks for Test Conditions	Groups of 10 male and 10 female Swiss mice were administered 250, 500, or 1000 mg/kg bw/day in paraffin oil by gavage for 2 consecutive days. Another group of 15 male and 15 female mice received one dose of 1000 mg/kg bw in paraffin oil by gavage. Control groups of mice (10/sex) were given paraffin oil only. Positive controls (4 mice/sex) were

	paraffin oil only. Positive controls (4 mice/sex) were administered 75 mg/kg bw of cyclophosphamide. About half of the mice receiving 2 treatments and the negative controls were killed on day 3 and the other half were killed on day 4. Mice given cyclophosphamide were killed on day 3 and those receiving only 1 dose of cumene were killed (5/sex/day) on days 2, 3, and 4. Clinical signs, survival and body weights were recorded. Bone marrow samples were stained, examined microscopically, and polychromatic erythrocytes (1,000/mouse) were evaluated. Results were considered positive if there was a dose-related statistically significant (p less than 0.05) increase in micronucleated polychromatic erythrocytes. The results would be considered equivocal if the response was dose-related OR statistically significant.
Appropriate statistical evaluations?	Student's t-test
Effect on mitotic index or PCE/NCE ratio by dose level and sex	The PCE/NCE ratios for paraffin oil, 0.25, 0.5, or 1000 mg/kg bw/day of cumene and cyclophosphamide were, respectively, 0.8, 0.8, 0.8, 0.8, 0.8, and 0.4 for males killed on day 3; 0.9, 0.8, 0.8, 0.8, 0.8, and NA for males killed on day 4; 0.8, 0.8, 0.8, 0.8, 0.9, and 0.4 for females killed on day 3; 0.8, 0.8, 0.8, 0.8, 0.9, and NA for females killed on day 4.
Genotoxic effects	There was no significant increase in micronuclei.
NOEL (C)/ LOEL (C)	1000 mg/kg
Remarks for Results	One female died in the negative control group.
Conclusion Remarks	Cumene did not induce micronuclei in mice.
Data Qualities Reliabilities	Reliability code 1. Reliable without restriction.
Remarks for Data Reliability	Code 1. Comparable to guideline study.
References	Khan S.H. (1985) Micronucleus test of cumene. Project #84-2129. Gulf Life Sciences Center. Unpublished report.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue cumene
Method/guideline	Micronucleus assay
Test Type	Clastogenic study
GLP	Yes
Year	1994
Species/Strain	F344 rat
Sex	Male
Route of Administration	Intraperitoneal

Doses/Concentration	78.13, 156.25, 312.5, 625, 1,250, or 2500 mg/kg bw
Exposure Period	72 hours
Remarks for Test Conditions	Groups of 5 male rats were administered 78.13, 156.25, 312.5, 625, 1250, or 2500 mg/kg bw by intraperitoneal injection daily for 72 hours. Control rats received corn oil vehicle or, as a positive control, 25 mg/kg bw of cyclophosphamide. Bone marrow cells from the femur of each rat were sampled 24 hours after the last exposure. Two thousand polychromatic erythrocytes were scored for frequency of micronucleated cells in each test animal.
Appropriate statistical evaluations?	Not described.
Effect on mitotic index or PCE/NCE ratio by dose level and sex	At the highest dose, 3/5 rats died. The average number of micronucleated cells per 1,000 polychromatic erythrocytes was 0.5, 17.3, 1.2, 1.2, 1.3, 0.8, 2.6, and 1.3 for corn oil vehicle, positive control, and 8.13, 156.25, 312.5, 625, 1250, or 2500 mg/kg bw of cumene, respectively. The slight increase in % PCE's/MN was not dose related.
Genotoxic effects	Induction of micronuclei
Remarks for Results	The authors reported a weak positive polychromatic erythrocyte trend of P = 0.011. Based on the total number of micronuclei/dose (control, 5; positive control, 173; 78 mg/kg, 12; 156 mg/kg, 12; 312 mg/kg, 13; 625 mg/kg, 8; 1250 mg/kg, 26) significant increase in micronuclei occurred at or near toxic dose levels.
Conclusion Remarks	It was concluded that cumene provided a weak induction of micronuclei in F344 rats.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	National Toxicology Program (NTP) (1994) In vivo Cytogenetics Testing. Micronucleus Induction Results. Unpublished report.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue cumene
Method/guideline	Micronucleus assay
Test Type	Clastogenic study
GLP	Yes
Year	1994
Species/Strain	F344 rat
Sex	Male
Route of Administration	Intraperitoneal

Doses/Concentration	312, 625, 1,250, or 2,500 mg/kg bw
Exposure Period	72 hours
Remarks for Test Conditions	Groups of 5 male rats were administered daily doses of 312, 625, 1250, or 2500 mg/kg bw of cumene by intraperitoneal daily for 72 hours. Control rats received corn oil vehicle or, as a positive control, 25 mg/kg bw of cyclophosphamide. Bone marrow cells from the femur of each rat were sampled 24 hours after the last exposure. Two thousand polychromatic erythrocytes were scored for frequency of micronucleated cells in each test animal. The study is a repeat of a study performed in 1994 (NTP, 1994)
Appropriate statistical evaluations?	Not described.
Effect on mitotic index or PCE/NCE ratio by dose level and sex	At the highest dose, 2/5 rats died. The average number of micronucleated cells per 1000 polychromatic erythrocytes was 0.5, 7.8, 1.7, 1.4, 1.8, and 1.5 for corn oil vehicle, positive control, and 312, 625, 1250, or 2500 mg/kg bw of cumene, respectively. There was no dose related increased in micronuclei over the dose range.
Genotoxic effects	Induction of micronuclei.
Remarks for Results	The authors reported a positive polychromatic erythrocyte trend of P = 0.085. Based on the total number of micronuclei/dose (control, 5; positive control, 78; 312 mg/kg, 17; 625 mg/kg, 13; 1250 mg/kg, 18) slight but significant increases in micronuclei occurred at all dose levels.
Conclusion Remarks	It was concluded that cumene provided a weak induction of micronuclei in F344 rats.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	National Toxicology Program (NTP) (1995) In vivo Cytogenetics Testing. Micronucleus Induction Results. Unpublished report.

4.3 Repeat dose Toxicity

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Purity greater than 99%
Method/guideline	Subacute inhalation neurotoxicity study
GLP	Ambiguous
Year	1996
Species/strain	Rat/Long Evans

Sex	Male
Route of Administration	Inhalation
Doses/concentration Levels	0, 50, or 250 ppm
Exposure Period	4 weeks
Frequency of Treatment	6 hr/day, 5 days/wk
Control Group	0 ppm
Post Exposure	8 weeks
Remarks for Test Conditions	This study was designed to specifically examine the neurotoxic potential of inhaled p-cymene. Rats were housed 2 per cage and subjected to a 12-hour light cycle. Exposure to p-cymene vapor occurred during the dark cycle and rats were placed in stainless steel wire cages without food or water. Air exchange in the exposure chambers was 13 times/hour with a temperature of 23 +\- 2 C. p-Cymene concentration in the exposure chamber was measured every 10 minutes with an infrared gas cell spectrophotometer. During the study, body weight was recorded weekly. After the 8-week recovery period, rats were decapitated and the cerebellum was removed, weighed, and homogenized (4 ml ice cold 0.32 M sucrose). The remainder of the brain was also weighed and homogenized. Synaptosomes were prepared using gradient centrifugation. The 2 homogenates and the synaptosomes were processed for neurotransmitter analyses (i.e., determination of noradrenaline [NA], dopamine [DA], and 5-hydroxytryptamine [5-HT]), and aliquots were taken for determination of enzyme activities (lactate dehydrogenase [LDH], acetylcholinesterase [AChE], and butylnylcholinesterase [BuChE]) and protein analysis.
NOAEL (NOEL)	250 ppm
Toxic Response/effects by Dose Level	The authors reported that there was no overt toxicity in the treated rats and no effect on body weight or terminal weight of the brain, cerebellum or whole brain. There was also no effect on regional enzyme activities, regional protein synthesis or regional neurotransmitter concentrations. The relative yield and total amount of synaptosomal protein were significantly reduced at 50 and 250 ppm in a concentration-related manner. Relative yield for control, 50 and 250 ppm = 16.4, 9.20, and 8.62 mg protein/g whole brain-cerebellum, respectively. Total amount for control 50, and 250 ppm = 29.1, 16.4, and 15.1 mg protein/g whole brain-cerebellum, respectively. The relative activity of LDH, AChE, and BuChE were significantly increased at 50 and 250 ppm. For control, 50 and 250 ppm, respectively: relative LDH activity = 2,7, 4.87, and 5.33 U/mg protein; relative AChE activity = 159, 291, and 288 mU/mg protein; relative BuChE activity = 209, 386, and 358 mU/mg protein. Total activity of LDH, AChE and BuChE were unaffected. In relation to the cytoplasmatic marker (LDH), the relative synaptosomal choline esterase activities (AChE and BuChE) were unaffected by p-cymene exposure. In relation to LDH, the relative synaptosomal concentrations of NA, DA, and 5-HT were unaffected by treatment. Relative to synaptosomal protein, relative NA and

	treatment. Relative to synaptosomal protein, relative NA and DA concentrations were significantly increased at 50 and 250 ppm; whereas 5-HT was unaffected. For control, 50, and 250 ppm, respectively: relative NA = 18.4, 34.4, and 31.3 pmol/mg synaptosomal protein; relative DA = 19.8, 38.0, and 36.8 pmol/mg synaptosomal protein; relative 5-HT = 8.98, 12.4, and 13.1 pmol/mg synaptosomal protein. Conversely, the total amount of NA and DA in the synaptosomal fraction was unaffected by treatment; whereas, the total amount of 5-HT was significantly decreased at 250 ppm. For control, 50, and 250 ppm, respectively: total amount of NA = 522, 544, and 461 pmol/whole brain-cerebellum; total amount of DA = 553, 600, and 541 pmol/whole brain-cerebellum; total amount of 5-HT = 255, 194, and 189 pmol/whole brain-cerebellum.
Statistical Evaluation	Yes. SAS program. Analysis of variance followed by Dunnett's two-tailed test when indicated. Significance P less than0.05.
Conclusion Remarks	At up to 250 ppm, p-cymene exposure did not produce signs of overt toxicity in male rats exposed for 4 weeks with an 8-week recovery period. Although, some statistically significant changes were noted in the synaptosomal fraction of homogenized brain, no generally accepted test system has been established for predicting neurotoxicity.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Lam H.R., Ladefoged, O., Ostergaard, G., Lund, S.P., and Simonsen, L. (1996) Four weeks' inhalation exposure of rats to p-cymene affects regional and synaptosomal neurochemistry. Pharmacol Toxicol., 79, 225-230.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue cumene; purity greater than 98%
Method/guideline	Gavage 6-month study
GLP	No
Year	1956
Species/strain	Rat/Wistar
Sex	Female
Route of Administration	Oral-Gavage
Doses/concentration Levels	154, 462, or 769 mg/kg bw/day in olive oil
Exposure Period	194 days
Frequency of Treatment	Daily, 5 days/week
Control Group	Gavaged with 2.5 ml olive oil (vehicle)

Post Exposure	None
Remarks for Test Conditions	Groups of 10 female Wistar rats were gavaged with 154, 462, or 769 mg cumene/kg bw/day in olive oil emulsified with gum arabic, 5 days/week for a period of 6 months. Twenty control rats were gavaged with the vehicle. Body weight, food consumption, growth, and mortality were monitored and recorded regularly. Animals alive at the end of the study were killed 18-22 hours following the last exposure. Selected animals were used for sampling of oxalated blood for BUN determination, and for bone marrow counts. Hematological examinations (i.e., total erythrocytes and leucocytes, hemoglobin content, and differential white blood cell count) were conducted on selected animals typically after 20, 40, 80, and 130 doses. At necropsy, animals underwent gross examination and the lungs, heart, liver, kidneys, and spleen were weighed and prepared for microscopic evaluation. Similarly, sections of the adrenals, pancreas, and femoral bone marrow were examined.
NOAEL (NOEL)	154 mg/kg bw/day
LOAEL (LOEL)	462 mg/kg bw/day
Actual dose received by dose level and sex	0, 154, 462, or 769 mg/kg bw/day
Toxic Response/effects by Dose Level	No effects were reported at the lowest dose. The only effects reported in the higher 2 doses was an increase in average kidney weight (not specified if absolute or relative weight): reported as "slight effect" at 462 mg/kg bw/day and "moderate effect" at 769 mg/kg bw/day. The reported increase was not accompanied by histopathological renal changes.
Statistical Evaluation	Yes. Fisher t-test.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Wolf M.A., Rowe, V.K., McCollister, D.D., Hollingsworth, R.L., and Oyen, F. (1956) Toxicological studies of certain alkylated benzenes and benzene. AMA Arch Ind Health, 14, 387-398.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue cumene
GLP	No
Year	1970
Species/strain	Squirrel monkey (*Saimiri sciurea*)
Sex	Male
Route of Administration	Inhalation

Doses/concentration Levels	244 ppm (1,195 mg/m3)
Exposure Period	30 exposures (i.e., 6 weeks)
Frequency of Treatment	8 hours/day, 5 days/week
Control Group	0 ppm
Post Exposure	None
Remarks for Test Conditions	Three male squirrel monkeys were exposed to atmospheres containing 244 ppm cumene, 8 hours/day, 5 days/week for a total of 30 exposures. The control group consisted of 12 monkeys. At the end of the exposures, animals were killed and necropsied with heart, lung, liver, spleen, brain, spinal cord, and kidney sections taken for histological examination.
NOAEL (NOEL)	244 ppm (1,195 mg/m3)
Toxic Response/effects by Dose Level	Body weight gain did not appear to be affected by cumene exposure and no histopathological effects were reported.
Statistical Evaluation	No
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Jenkins L.J., Jr., Jones, R.A., and Siegel, J. (1970) Long-term inhalation screening studies of benzene, toluene, o-xylene, and cumene on experimental animals. Toxicol Appl Pharmacol., 16, 818-823.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue cumene
GLP	No
Year	1970
Species/strain	Rat/Sprague-Dawley or Long Evans
Sex	Male and Female
Route of Administration	Inhalation
Doses/concentration Levels	3.7 or 30 ppm (18 or 146 mg/m3)
Exposure Period	90 days
Frequency of Treatment	Continuous
Control Group	0 ppm
Post Exposure	None

Remarks for Test Conditions	Groups of 14-15 rats (males and females, ratio not stated) were exposed to atmospheres containing 0, 3.7, or 30 ppm cumene continuously for a period of 90 days. At the end of the exposures, animals were killed and necropsied with heart, lung, liver, spleen, and kidney sections taken for histological examination. Blood samples also were taken for hematological evaluation (i.e., leukocyte count, hemoglobin, and hematocrit).
LOAEL (LOEL)	3.7 ppm (18 mg/m3)
Toxic Response/effects by Dose Level	One rat died on day 11 in the 3.7 ppm group (no further details were given). Body weight gain did not appear to be affected by cumene exposure and no histopathological effects were reported. Although statistical analysis was not conducted, an increase in the number of leukocytes was reported following cumene exposure. Aside from a slight decrease in hematocrit, no other effects on hematological parameters were apparent.
Statistical Evaluation	No
Remarks for Results	The increased number of leukocytes appears to be consistent with the results of Cushman et al. (1995) and therefore was considered by the reviewer (and EPA, 1997) to be the basis of the LOAEL.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Jenkins L.J., Jr., Jones, R.A., and Siegel, J. (1970) Long-term inhalation screening studies of benzene, toluene, o-xylene, and cumene on experimental animals. Toxicol Appl Pharmacol., 16, 818-823..

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue cumene; purity greater than 99.9%
Method/guideline	Inhalation toxicity
GLP	Yes
Year	Undated
Species/strain	Mouse/B5C3F1
Sex	Male and Female
Route of Administration	Inhalation
Doses/concentration Levels	250, 500, 1,000, 2,000, or 4,000 ppm
Exposure Period	13 days over a 17-day period
Frequency of Treatment	Daily
Control Group	0 ppm

Post Exposure	None
Remarks for Test Conditions	Groups of 5 male and 5 female B5C3F1 mice were exposed to target concentrations of 0, 250, 500, 1,000, 2,000, or 4,000 ppm cumene by whole-body inhalation for 13 days over a period of 17 days. Cumene vapor was distributed into exposure chambers using a single vapor generator delivery subsystem and vapor distribution manifold. A metering valve was used to control vapor delivery and cumene vapor was diluted or mixed with conditioned chamber air prior to entry into the exposure chamber. The exposure chambers were monitored every 20 minutes. Animals were observed for survival, clinical signs, and body weight changes. At study termination, any organ weight changes or histopathological effects were noted.
NOAEL (NOEL)	500 ppm (females); 1,000 ppm (males)
LOAEL (LOEL)	1,000 ppm (females); 2,000 ppm (males)
Toxic Response/effects by Dose Level	All mice exposed to 2,000 or 4,000 ppm died by day 2. At 1,000 ppm, 4/5 females were dead by day 4. All remaining animals survived to study termination. Male mice exposed to 1,000 ppm showed varying degrees of ataxia, which was most severe during week 1. Body weight of surviving animals was similar to controls. Relative liver weight was significantly increased in male and female mice exposed to 250 ppm and higher. Absolute liver weight was significantly increased in males exposed to 250 ppm and higher and in females exposed to 500 ppm and higher. In females, absolute and relative kidney weight was significantly increased at 1,000 ppm; whereas in males, absolute kidney weight was significantly increased only at 250 ppm and relative kidney weight was significantly increased at 250 and 500 ppm. Absolute and relative thymus weight was significantly decreased at 1,000 ppm in males (no data for females). No histopathological findings accompanied the organ weight changes.
Statistical Evaluation	Not described.
Remarks for Results	During the study period, cumene was stable and uniform in the exposure chambers and the test concentrations remained within the protocol specified range for daily means with acceptable relative standard deviations.
Conclusion Remarks	Based on these results, NTP set exposure concentrations of 62.5 to 1,000 ppm cumene for the 13-week inhalation study. The NOAELs were based on mortality and lack of histopathology.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	NTP unpublished results (c). 2-Week Inhalation Toxicity Study of Cumene--Mice. National Toxicology Program.

Substance Name	*p*-Cymene
CAS No.	99-87-6

Remarks for Substance	Data for homologue cumene; purity greater than 99.9%
Method/guideline	Subchronic inhalation study
GLP	Yes
Year	Undated
Species/strain	Mouse/B6C3F1
Sex	Male and Female
Route of Administration	Inhalation
Doses/concentration Levels	62.5, 125, 250, 500, or 1,000 ppm
Exposure Period	13 weeks
Frequency of Treatment	6 hours/day plus T90, 5 days/week
Control Group	0 ppm
Post Exposure	None
Remarks for Test Conditions	Groups of 10 male and 10 female B6C3F1 mice were exposed to target concentrations of 0, 62.5, 125, 250, 500 or 1,000 ppm cumene by whole-body inhalation 6 hours/day plus T90, 5 days/week for up to 13 weeks. Cumene vapor was distributed into exposure chambers using a single vapor generator delivery subsystem and vapor distribution manifold. A metering valve was used to control vapor delivery and cumene vapor was diluted or mixed with conditioned chamber air prior to entry into the exposure chamber. The exposure chambers were monitored every 20 minutes. Animals were observed for survival, clinical signs, and body weight changes. At study termination, any organ weight changes or histopathological effects were noted. Hematology also was evaluated but not described in detail.
NOAEL (NOEL)	250 ppm
LOAEL (LOEL)	500 ppm
Toxic Response/effects by Dose Level	All male mice survived to the end of the study. Eight out of 10 female mice exposed to 1,000 ppm cumene died within the first week of exposure. Transient signs of ataxia were reported in high-dose males and surviving females during the first week of exposure. Male mice at the 2 highest exposures showed statistically significant decreased final body weights; whereas female final body weights were not affected. Absolute liver weight was significantly increased at 1,000 ppm in both sexes. Relative liver weight was significantly increased in all exposed males and in females exposed to 250 ppm cumene and higher. No effect on hematology was reported. Histopathologically, centrilobular hypertrophy of the liver was reported in all males exposed to 1,000 ppm cumene. No other males (treated or controls) had similar findings. In females, squamous hyperplasia and inflammation of the mucosa of the forestomach were reported at 500 and 1,000 ppm (2/10 and 1/10 rats, respectively) compared to no forestomach lesions in controls.

	respectively) compared to no forestomach lesions in controls.
Statistical Evaluation	Not described.
Remarks for Results	During the study period, cumene was stable and uniform in the exposure chambers and the test concentrations remained within the protocol specified range for daily means with acceptable relative standard deviations.
Conclusion Remarks	A NOAEL of 250 ppm was determined based on mortality, body weight changes, and histopathological findings.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	NTP unpublished results (a). 13-Week Subchronic Inhalation Toxicity Study of Cumene--Mice. National Toxicology Program.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue cumene; purity greater than 99.9%
Method/guideline	Subchronic inhalation study
GLP	Yes
Year	Undated
Species/strain	Rat/F344/N
Sex	Male and Female
Route of Administration	Inhalation
Doses/concentration Levels	62.5, 125, 250, 500, or 1,000 ppm
Exposure Period	13 weeks
Frequency of Treatment	6 hours/day plus T90, 5 days/week
Control Group	0 ppm
Post Exposure	None
Remarks for Test Conditions	Groups of 20 male and 20 female F344/N rats were exposed to target concentrations of 0, 62.5, 125, 250, 500 or 1,000 ppm cumene by whole-body inhalation 6 hours/day plus T90, 5 days/week for up to 13 weeks. Cumene vapor was distributed into exposure chambers using a single vapor generator delivery subsystem and vapor distribution manifold. A metering valve was used to control vapor delivery and cumene vapor was diluted or mixed with conditioned chamber air prior to entry into the exposure chamber. The exposure chambers were monitored every 20 minutes. Animals were observed for survival, clinical signs, and body weight changes. At study termination, any organ weight changes or histopathological effects were noted. Hematology and clinical chemistry also

	effects were noted. Hematology and clinical chemistry also were evaluated but not described in detail.
NOAEL (NOEL)	125 ppm
LOAEL (LOEL)	250 ppm
Toxic Response/effects by Dose Level	All animals survived to study termination without any significant effect on final body weights. Mild ataxia was observed in high-dose animals during the initial days of exposure. In males exposed to 250 ppm and higher, absolute and relative liver weight and absolute kidney weight were significantly increased. Relative kidney weight was significantly increased in all exposed males. In females, relative liver weight was increased at the 3 highest concentrations; whereas relative kidney weight was increased at the 2 highest exposure concentrations. The effect on hematology parameters was reported as "not remarkable" and the most notable serum chemistry result was increased total bile acid concentration on days 3 (concentrations of 125 ppm and higher) and 23 (concentrations of 250 ppm and higher) in both sexes. At terminal sacrifice, a significant decrease in alanine aminotransferase was reported in males and females exposed to 250 ppm cumene and higher. Accompanying the kidney weight increase in males was an increase in hyaline droplets and tubular regeneration in renal cortical tubules and granular casts in tubules in the corticomedullary junction area. The severity and incidence of granular casts was reported to show an exposure-related response. These findings were not reported in females. The amount of *alpha*-2u-globulin in the kidney of male rats increased in an exposure-related manner, reaching statistical significance at concentrations of 125 ppm and higher. Proliferating cell nuclear antigen was measured and showed no difference from controls indicating that there was no difference in renal cortical cell turnover rates. No other histopathological findings were reported.
Statistical Evaluation	Not described.
Remarks for Results	During the study period, cumene was stable and uniform in the exposure chambers and the test concentrations remained within the protocol specified range for daily means with acceptable relative standard deviations. The renal lesions reported in the male rats were considered by the conducting laboratory to be similar to those "resulting from exposure to chemicals that induce accumulation of *alpha*-2u-globulin in renal cortical tubular cytoplasm".
Conclusion Remarks	A NOAEL of 125 ppm was determined for both sexes based on serum chemistry, organ weight changes, and renal changes reported in males.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	NTP unpublished results (b). 13-Week Subchronic Inhalation Toxicity Study of Cumene--Rats. National Toxicology Program.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue cumene; purity greater than 99.9%
Method/guideline	Subchronic inhalation study
GLP	Yes
Year	Undated
Species/strain	Mouse/B6C3F1
Sex	Male and Female
Route of Administration	Inhalation
Doses/concentration Levels	62.5, 125, 250, 500, or 1,000 ppm
Exposure Period	13 weeks
Frequency of Treatment	6 hours/day plus T90, 5 days/week
Control Group	0 ppm
Post Exposure	None
Remarks for Test Conditions	Groups of 10 male and 10 female B6C3F1 mice were exposed to target concentrations of 0, 62.5, 125, 250, 500 or 1,000 ppm cumene by whole-body inhalation 6 hours/day plus T90, 5 days/week for up to 13 weeks. Cumene vapor was distributed into exposure chambers using a single vapor generator delivery subsystem and vapor distribution manifold. A metering valve was used to control vapor delivery and cumene vapor was diluted or mixed with conditioned chamber air prior to entry into the exposure chamber. The exposure chambers were monitored every 20 minutes. Animals were observed for survival, clinical signs, and body weight changes. At study termination, any organ weight changes or histopathological effects were noted. Hematology also was evaluated but not described in detail.
NOAEL (NOEL)	250 ppm
LOAEL (LOEL)	500 ppm
Toxic Response/effects by Dose Level	All male mice survived to the end of the study. Eight out of 10 female mice exposed to 1,000 ppm cumene died within the first week of exposure. Transient signs of ataxia were reported in high-dose males and surviving females during the first week of exposure. Male mice at the 2 highest exposures showed statistically significant decreased final body weights; whereas female final body weights were not affected. Absolute liver weight was significantly increased at 1,000 ppm in both sexes. Relative liver weight was significantly increased in all exposed males and in females exposed to 250 ppm cumene and higher. No effect on hematology was reported. Histopathologically, centrilobular hypertrophy of the liver was reported in all males exposed to 1,000 ppm cumene. No other males (treated or

	exposed to 1,000 ppm cumene. No other males (treated or controls) had similar findings. In females, squamous hyperplasia and inflammation of the mucosa of the forestomach were reported at 500 and 1,000 ppm (2/10 and 1/10 rats, respectively) compared to no forestomach lesions in controls.
Statistical Evaluation	Not described.
Remarks for Results	During the study period, cumene was stable and uniform in the exposure chambers and the test concentrations remained within the protocol specified range for daily means with acceptable relative standard deviations.
Conclusion Remarks	A NOAEL of 250 ppm was determined based on mortality, body weight changes, and histopathological findings.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	NTP unpublished results(a). 13-Week Subchronic Inhalation Toxicity Study of Cumene--Mice. National Toxicology Program.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue cumene; purity greater than 99.9%
Method/guideline	Inhalation toxicity
GLP	Ambiguous
Year	1995
Species/strain	Rat/Fischer 344/NHSD
Sex	Male and Female
Route of Administration	Inhalation
Doses/concentration Levels	50, 100, 500, or 1,200 ppm
Exposure Period	13 weeks
Frequency of Treatment	6 hours/day, 5 days/week
Control Group	0 ppm
Post Exposure	4 weeks
Remarks for Test Conditions	Groups of 15 male and 15 female rats were exposed to atmospheres containing 0, 50, 100, 500, or 1,200 ppm cumene 6 hours/day, 5 days/week for 13 weeks plus 2 or 3 days followed by a 4-week recovery period. Rats were individually exposed to test atmospheres in wire-mesh exposure cages in 900-L rectangular glass and stainless steel chambers with an airflow rate of 200 liter/minute with 13 air changes/hour. Chamber temperature, relative humidity, and cumene concentration (measured by GC) were measured every half hour during the 6-hour exposure. When not in the exposure

	hour during the 6-hour exposure. When not in the exposure chambers, the rats were individually housed and maintained on a 12-hour photoperiod and had ad libitum access to basal rodent diet and water. During the study, cages were rotated within the exposure chamber and non-exposure housing to ensure uniform exposures to the test material and lighting. Rats were observed daily on exposure days for clinical signs and on non-exposure days for mortality. Body weight was measured weekly. Fifteen rats/sex were tested for motor activity prior to exposure and on the weekends following study weeks 4, 9, and 13 using an automated recording apparatus. Test sessions lasted 90 min with intrasession intervals of 10 min. Ten rats/sex were assessed for tone-pip auditory brain stem responses during post exposure week 1. Eyes were examined by 2 independent veterinary ophthalmologists pre-exposure, at weeks 4, 9, and 13 and during post exposure week 4. All rats were necropsied and liver, kidney, lungs, adrenal, gonad and brain weights were measured. In this study, only the eyes were histopathologically examined.
NOAEL (NOEL)	500 ppm
LOAEL (LOEL)	1,200 ppm
Actual dose received by dose level and sex	Test concentrations within 1% of target
Toxic Response/effects by Dose Level	Motor activity was not affected in cumene-exposed rats. Mean body weights were similar between test and control animals, although there was a transient decrease in body weight gain in both sexes exposed to 1,200 ppm cumene during week 1. There were no differences between test and control animals for tone-pip auditory brain stem responses. No treatment-related cataracts were reported in this study. Absolute and relative liver weights were statistically increased in males exposed to 500 ppm cumene and females exposed to 1,200 ppm cumene. Only absolute liver weight was statistically increased in males exposed to 1,200 ppm cumene. Relative kidney weights and absolute and relative adrenal gland weights were statistically increased only in females exposed to 1,200 ppm cumene.
Statistical Evaluation	Yes. Levene's test for equal variances, ANOVA, t tests, repeated-measures analysis (Dixon, 1985), Fisher's exact test, MANOVA with use of GLM procedure of SAS, F test based on Hotelling-Lawley trace statistics, F-max test.
Remarks for Results	The EPA (1997) evaluated the results of this study and established a NOAEL of 496 ppm and a LOAEL of 1,202 ppm based on relative and absolute weight alterations that were both biologically and statistically significant. The changes in liver weight were considered by EPA (1997) not to be toxicologically relevant since they were not accompanied by histopathology (demonstrated in the first study from this publication).
Conclusion Remarks	Cumene was not ototoxic in this study.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.

References	Cushman J.R., Norris, J.C., Dodd, D.E., Darmer, K.I., Morris, C.R. (1995) Subchronic inhalation toxicity and neurotoxicity assessment of cumene in Fischer 344 rats. J Am Coll Toxicol., 14(2), 129-147.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue cumene; purity greater than 99.9%
Method/guideline	Inhalation toxicity
GLP	Ambiguous
Year	1995
Species/strain	Rat/Fischer 344/NHSD
Sex	Male and Female
Route of Administration	Inhalation
Doses/concentration Levels	100, 500, or 1,200 ppm
Exposure Period	13 weeks
Frequency of Treatment	6 hours/day, 5 days/week
Control Group	0 ppm
Post Exposure	None
Remarks for Test Conditions	Groups of 21 male and 21 female rats were exposed to atmospheres containing 0, 100, 500, or 1,200 ppm cumene 6 hours/day, 5 days/week for 13 weeks plus 2 or 3 days. Rats were individually exposed to test atmospheres in wire-mesh exposure cages in 4,300-L rectangular glass and stainless steel chambers with an airflow rate of approximately 900 liter/minute with 12.5 air changes/hour. Chamber temperature, relative humidity, and cumene concentration (measured by GC) were measured every half hour during the 6-hour exposure. When not in the exposure chambers, the rats were individually housed and maintained on a 12-hour photoperiod and had ad libitum access to basal rodent diet and water. During the study, cages were rotated within the exposure chamber and non-exposure housing to ensure uniform exposures to the test material and lighting. Rats were observed daily on exposure days for clinical signs and on non-exposure days for mortality. Body weight and food and water consumption were determined weekly. Ten rats of both sexes underwent a functional observational battery and 15 rats/sex were tested for motor activity prior to exposure and on the weekends following study weeks 1, 2, (behavioral only), 4, 9, and 13 using an automated recording apparatus. Test sessions lasted 90 min with intrasession intervals of 10 minutes. Eyes were examined during week 13. Five rats/sex/group were selected for hematology and serum chemistry prior to exposure and 10 rats/sex/group were

chemistry prior to exposure and 10 rats/sex/group were sampled during week 13. Parameters examined included erythrocyte, platelet, leukocyte, differential leukocyte, and reticulocyte (males only) counts, hemoglobin, hematocrit, mean corpuscular volume, hemoglobin and hemoglobin concentration, glucose, urea nitrogen, creatinine, total protein, albumin, globulin, bilirubin, calcium, phosphorus, sodium, potassium, chloride, aspartate and alanine aminotransferases, and gamma-glutamyltransferase. At study termination, 6 rats/sex/group were selected for microscopic evaluation of the brain, spinal cord, and peripheral nerves. All remaining rats were necropsied and liver, kidney, lungs, adrenal, gonad and brain weights were measured. In addition to microscopic examination of standard tissues from high-dose rats, lung tissues from both the 100 and 500 ppm groups were examined and kidney sections from all male rats were evaluated for tubular hyaline droplet formation. In addition, to evaluate sperm count and sperm morphology, the epididymides of 15 male rats/group were removed. Also, the right testis of each male was frozen and homogenized to count spermatid by the method of Johnson et al. (1980) and Blazak et al. (1985). In the high-dose and control groups, the right testis of each male rat was evaluated for the stages of spermatogenesis according to the method of Land and Chapin (1985).

NOAEL (NOEL) 500 ppm

LOAEL (LOEL) 1,200 ppm

Actual dose received by dose level and sex Test concentrations within 1% of target

Toxic Response/effects by Dose Level At 1,200 ppm, 1 male rat was killed moribund due to a caging accident, rats showed ataxia following the first 2-3 weeks, rats "appeared hypoactive, exhibited blepharospasm, and showed a delayed or absent startle reflex". In both the 500 and 1,200 ppm groups, rats "showed increased incidences of periocular tissue swelling, urine stains, urogenital area wetness, and/or perinasal encrustation. Rats exposed to 500 ppm also were hypoactive. Exposed rats showed no differences in the functional observational battery. At week 13, males rats exposed to 500 or 1,200 ppm cumene showed a decrease in total motor activity (i.e., fine movement, rearing, and ambulation combined). More specifically, there was a statistically significant decrease in ambulatory activity at weeks 4, 9, and 13. Mean body weights were similar for all groups; however, there was a transient decrease in body weight gain of high-dose females during week 1, 2, 6, and 7. In addition, mean food consumption was decreased at week 1 in females exposed to 500 and 1,200 ppm cumene. Water consumption was consistently increased (by 40% over controls) in male and female rats throughout most of the study. Cataracts were observed in about 14-55% of all groups (including controls). With respect to hematology and blood chemistry, leukocytes and platelets were significantly increased at the 2 highest concentrations in both sexes and lymphocytes were significantly increased at the 2 highest concentrations in males only. Glucose was significantly decreased in females of the 500 and 1,200 ppm groups, but not in males. Total protein, albumin and globulin were significantly

	in males. Total protein, albumin and globulin were significantly increased in both sexes exposed to 1,200 ppm. Calcium and inorganic phosphorus were significantly increased at 1,200 ppm in both sexes and at 500 ppm in males. At 1,200 ppm, both males and females had significantly increased absolute and relative liver, kidney, and adrenal gland weights. Absolute and relative liver weight also was significantly increased in both sexes exposed to 500 ppm cumene. Significantly increased relative kidney weight and absolute adrenal gland weight was reported in females and males, respectively, at 500 ppm. There were no effects reported in the examination of nervous system tissue in any of the groups. The only microscopic findings reported were in the kidneys of males rats exposed to 500 or 1,200 ppm cumene. Tubular proteinosis was significantly increased in high-dose males, and interstitial nephritis and tubular cell hyperplasia/hypertrophy were significantly increased at both 500 and 1,200 ppm cumene. In addition, at the 2 highest concentrations, an increase in hyaline droplet formation within the proximal tubules of male rats was reported. Testicular sperm head and epididymal spermatozoa counts were similar for all groups and there was no effect on epididymal sperm morphology.
Statistical Evaluation	Yes. Levene's test for equal variances, ANOVA, t tests, repeated-measures analysis (Dixon, 1985), Fisher's exact test.
Remarks for Results	The decreased motor activity was not replicated in a second study under the same conditions, but including a 4-week recovery period. The cataracts observed in this study were considered uninterruptible, but in a second similar study were determined by ophthalmologists to be unrelated to cumene exposure. The EPA (1997) evaluated the results of this study and established a NOAEL of 496 ppm and a LOAEL of 1,202 ppm based on relative and absolute weight alterations that were both biologically and statistically significant. The changes in liver weight were considered by EPA (1997) not to be toxicologically relevant since they were not accompanied by histopathology. The blood effects reported were also considered irrelevant since they were within normal ranges.
Conclusion Remarks	Exposure to cumene at concentrations below 1,200 ppm produced no adverse effects in rats over a 13-week period.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Cushman J.R., Norris, J.C., Dodd, D.E., Darmer, K.I., Morris, C.R. (1995) Subchronic inhalation toxicity and neurotoxicity assessment of cumene in Fischer 344 rats. J Am Coll Toxicol., 14(2), 129-147.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue cumene

GLP	No
Year	1970
Species/strain	Guinea pig/Princeton-derived
Sex	Male and Female
Route of Administration	Inhalation
Doses/concentration Levels	3.7 or 30 ppm (18 or 146 mg/m3)
Exposure Period	90 days
Frequency of Treatment	Continuous
Control Group	0 ppm
Post Exposure	None
Remarks for Test Conditions	Groups of 15 guinea pigs (males and females, ratio not stated) were exposed to atmospheres containing 0, 3.7, or 30 ppm cumene continuously for a period of 90 days. At the end of the exposures, animals were killed and necropsied with heart, lung, liver, spleen, and kidney sections taken for histological examination. Blood samples also were taken for hematological evaluation (i.e., leukocyte count, hemoglobin, and hematocrit).
NOAEL (NOEL)	3.7 ppm (18 mg/m3)
LOAEL (LOEL)	30 ppm (146 mg/m3)
Toxic Response/effects by Dose Level	Body weight gain appeared to be reduced in rats exposed to 30 ppm cumene, but increased in rats exposed to 3.7 ppm cumene. No histopathological effects were reported. No effects on hematological parameters were apparent.
Statistical Evaluation	No.
Remarks for Results	Without statistical analysis, it is difficult to interpret the significance of the findings particularly when these due not seem to be concentration related.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Jenkins L.J., Jr., Jones, R.A., and Siegel, J. (1970) Long-term inhalation screening studies of benzene, toluene, o-xylene, and cumene on experimental animals. Toxicol Appl Pharmacol., 16, 818-823.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue cumene
GLP	No

Year	1970
Species/strain	Dog/Beagle
Sex	Male
Route of Administration	Inhalation
Doses/concentration Levels	3.7 or 30 ppm (18 or 146 mg/m3)
Exposure Period	90 days
Frequency of Treatment	Continuous
Control Group	0 ppm
Post Exposure	None
Remarks for Test Conditions	Groups of 2 male beagle dogs were exposed to atmospheres containing 3.7, or 30 ppm cumene continuously for a period of 90 days. The control group consisted of 10 male beagle dogs. At the end of the exposures, animals were killed and necropsied with heart, lung, liver, spleen, brain, spinal cord, and kidney sections taken for histological examination. Blood samples also were taken for hematological evaluation (i.e., leukocyte count, hemoglobin, and hematocrit).
NOAEL (NOEL)	30 ppm (146 mg/m3)
Toxic Response/effects by Dose Level	Body weight gain did not appear to be affected by cumene exposure and no histopathological effects were reported. No effects on hematological parameters were apparent.
Statistical Evaluation	No
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Jenkins L.J., Jr., Jones, R.A., and Siegel, J. (1970) Long-term inhalation screening studies of benzene, toluene, o-xylene, and cumene on experimental animals. Toxicol Appl Pharmacol., 16, 818-823.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue cumene
GLP	No
Year	1970
Species/strain	Squirrel monkey (Saimiri sciurea)
Sex	Male

Route of Administration	Inhalation
Doses/concentration Levels	3.7 or 30 ppm (18 or 146 mg/m3)
Exposure Period	90 days
Frequency of Treatment	Continuous
Control Group	0 ppm
Post Exposure	None
Remarks for Test Conditions	Groups of 3 male squirrel monkeys were exposed to atmospheres containing 3.7, or 30 ppm cumene continuously for a period of 90 days. The control group consisted of 12 monkeys. At the end of the exposures, animals were killed and necropsied with heart, lung, liver, spleen, brain, spinal cord, and kidney sections taken for histological examination.
Toxic Response/effects by Dose Level	Terminal body weights were lower in treated animals than in controls when compared with starting body weights (starting body weight versus terminal body weight: 0 ppm, 690 g versus 679 g; 3.7 ppm, 759 g versus 687 g; 30 ppm, 755 g versus 644 g), but no histopathological effects were reported.
Statistical Evaluation	No
Remarks for Results	Without statistical analysis, it is difficult to interpret the significance of the findings particularly when similar effects were occurring in the control animals.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Jenkins L.J., Jr., Jones, R.A., and Siegel, J. (1970) Long-term inhalation screening studies of benzene, toluene, o-xylene, and cumene on experimental animals. Toxicol Appl Pharmacol., 16, 818-823.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue cumene; purity greater than 99.9%
Method/guideline	Inhalation toxicity
GLP	Yes
Year	Undated
Species/strain	Rat/F344/N
Sex	Male and Female
Route of Administration	Inhalation
Doses/concentration Levels	250, 500, 1,000, 2,000, or 4,000 ppm

Exposure Period	12 days over a 16-day period
Frequency of Treatment	Daily
Control Group	0 ppm
Post Exposure	None
Remarks for Test Conditions	Groups of 5 male and 5 female F344/N rats were exposed to target concentrations of 0, 250, 500, 1,000, 2,000, or 4,000 ppm cumene by whole-body inhalation for 12 days over a period of 16 days. Cumene vapor was distributed into exposure chambers using a single vapor generator delivery subsystem and vapor distribution manifold. A metering valve was used to control vapor delivery and cumene vapor was diluted or mixed with conditioned chamber air prior to entry into the exposure chamber. The exposure chambers were monitored every 20 minutes. Animals were observed for survival, clinical signs, and body weight changes. At study termination, any organ weight changes or histopathological effects were noted.
NOAEL (NOEL)	1,000 ppm (females)
LOAEL (LOEL)	500 ppm (females); 250 ppm (males)
Toxic Response/effects by Dose Level	All rats exposed to 4,000 ppm cumene died by day 1. At 2,000 ppm, 3/5 females and 2/5 males died by day 4. There was a significant decrease in mean body weight in rats exposed to 2,000 ppm cumene. Surviving rats exposed to 1,000 or 2,000 ppm cumene showed varying degrees of ataxia or lethargy, which was more severe at the beginning of the exposure week. At 500 ppm, mild ataxia was noted only after the first exposure. Relative liver weight was significantly increased in both sexes exposed to all test concentrations. Absolute liver weight was significantly increased in males exposed to 1,000 or 2,000 ppm and in females exposed to 500 ppm cumene or higher. Relative kidney weight was increased in both sexes at all test concentrations. Absolute kidney weight was significantly increased only at 250 and 1,000 ppm in males and at 250, 500 and 1,000 ppm in females. Absolute and relative thymus weight was significantly decreased at 2,000 ppm in both sexes. In exposed males, hyaline droplets in the renal cortical tubules were reported (incidences at 0, 250, 500, 1,000 and 2,000 ppm: 0/5, 3/5, 2/5, 3/5 and 1/5). None were observed in the 4,000 ppm group likely due to the short exposure period. At 2,000 ppm, suppurative inflammation of the lung was reported in 2/5 males and 2/5 females. One female rat exposed to 2,000 ppm cumene also had histiocytic cellular infiltrate of the lungs. Three out of 5 males exposed to 2,000 ppm cumene were reported to show liver congestion.
Statistical Evaluation	Not described.
Remarks for Results	During the study period, cumene was stable and uniform in the exposure chambers and the test concentrations remained within the protocol specified range for daily means with acceptable relative standard deviations.
Conclusion Remarks	Based on these results, NTP set exposure concentrations of 62.5 to 1,000 ppm cumene for the 13-week inhalation study. No NOAEL was determined for males because of mortality and

	No NOAEL was determined for males because of mortality and histopathology; however a NOAEL of 1,000 ppm was determined for females based on mortality and histopathological findings.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	NTP unpublished results (d). 2-Week Inhalation Toxicity Study of Cumene--Rats. National Toxicology Program.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue cumene
GLP	No
Year	1970
Species/strain	Rat/Sprague-Dawley or Long Evans
Sex	Male and Female
Route of Administration	Inhalation
Doses/concentration Levels	244 ppm (1,195 mg/m3)
Exposure Period	30 exposures (i.e., 6 weeks)
Frequency of Treatment	8 hours/day, 5 days/week
Control Group	0 ppm
Post Exposure	None
Remarks for Test Conditions	Groups of 14-15 rats (males and females, ratio not stated) were exposed to atmospheres containing 0 or 244 ppm cumene, 8 hours/day, 5 days/week for a total of 30 exposures. At the end of the exposures, animals were killed and necropsied with heart, lung, liver, spleen, and kidney sections taken for histological examination. Blood samples also were taken for hematological evaluation (i.e., leukocyte count, hemoglobin, and hematocrit).
LOAEL (LOEL)	244 ppm (1,195 mg/m3)
Toxic Response/effects by Dose Level	Body weight gain did not appear to be affected by cumene exposure and no histopathological effects were reported. Although statistical analysis was not conducted, an increase in the number of leukocytes was reported following cumene exposure. Aside from a slight decrease in hematocrit, no other effects on hematological parameters were apparent.
Statistical Evaluation	No
Remarks for Results	The increased number of leukocytes appears to be consistent with the results of Cushman et al. (1995) and therefore was considered by the reviewer (and EPA, 1997) to be the basis of

	considered by the reviewer (and EPA, 1997) to be the basis of the LOAEL.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Jenkins L.J., Jr., Jones, R.A., and Siegel, J. (1970) Long-term inhalation screening studies of benzene, toluene, o-xylene, and cumene on experimental animals. Toxicol Appl Pharmacol., 16, 818-823.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue cumene
GLP	No
Year	1970
Species/strain	Guinea pig/Princeton-derived
Sex	Male and Female
Route of Administration	Inhalation
Doses/concentration Levels	244 ppm (1,195 mg/m3)
Exposure Period	30 exposures (i.e., 6 weeks)
Frequency of Treatment	8 hours/day, 5 days/week
Control Group	0 ppm
Post Exposure	None
Remarks for Test Conditions	Groups of 15 guinea pigs (males and females, ratio not stated) were exposed to atmospheres containing 0 or 244 ppm cumene, 8 hours/day, 5 days/week for a total of 30 exposures. At the end of the exposures, animals were killed and necropsied with heart, lung, liver, spleen, and kidney sections taken for histological examination. Blood samples also were taken for hematological evaluation (i.e., leukocyte count, hemoglobin, and hematocrit).
LOAEL (LOEL)	244 ppm (1,195 mg/m3)
Toxic Response/effects by Dose Level	Body weight gain appeared to be reduced in cumene-exposed animals, but no histopathological effects were reported. No effects on hematological parameters were apparent.
Statistical Evaluation	No.
Remarks for Results	Without statistical analysis, it is difficult to interpret the significance of the findings particularly when these tendencies are not seen in the other animal species tested (rats, dogs, and monkeys).

Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Jenkins L.J., Jr., Jones, R.A., and Siegel, J. (1970) Long-term inhalation screening studies of benzene, toluene, o-xylene, and cumene on experimental animals. Toxicol Appl Pharmacol., 16, 818-823.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue cumene
GLP	No
Year	1970
Species/strain	Dog/Beagle
Sex	Male
Route of Administration	Inhalation
Doses/concentration Levels	244 ppm (1,195 mg/m3)
Exposure Period	30 exposures (i.e., 6 weeks)
Frequency of Treatment	8 hours/day, 5 days/week
Control Group	0 ppm
Post Exposure	None
Remarks for Test Conditions	Two male beagle dogs were exposed to atmospheres containing 244 ppm cumene, 8 hours/day, 5 days/week for a total of 30 exposures. The control group consisted of 10 male beagle dogs. At the end of the exposures, animals were killed and necropsied with heart, lung, liver, spleen, brain, spinal cord, and kidney sections taken for histological examination. Blood samples also were taken for hematological evaluation (i.e., leukocyte count, hemoglobin, and hematocrit).
LOAEL (LOEL)	244 ppm (1,195 mg/m3)
Toxic Response/effects by Dose Level	Body weight gain did not appear to be affected by cumene exposure and no histopathological effects were reported. There appeared to be an effect on the hematological parameters examined following cumene exposure: an increase in leukocytes, and increased hemoglobin and hematocrit.
Statistical Evaluation	No
Remarks for Results	Without statistical analysis, it is difficult to interpret the significance of the findings.
Conclusion Remarks	

Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Basic data given: comparable to guidelines/standards.
References	Jenkins L.J., Jr., Jones, R.A., and Siegel, J. (1970) Long-term inhalation screening studies of benzene, toluene, o-xylene, and cumene on experimental animals. Toxicol Appl Pharmacol., 16, 818-823.

4.4 Reproductive Toxicity

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue cumene; purity greater than 99.94%
Test Type	Inhalation toxicity
GLP	Ambiguous
Year	1995
Species/Strain	Rat/Fischer 344/NHSD
Sex	Male
Route of Administration	Inhalation
Duration of Test	13 weeks
Doses/Concentration	100, 500, or 1,200 ppm
Control Group and Treatment	0 ppm
Frequency of Treatment	6 hours/day, 5 days/week
Remarks for Test Conditions	As part of a subchronic study, groups of 21 male rats were exposed to atmospheres containing 0, 100, 500, or 1200 ppm cumene 6 hours/day, 5 days/week for 13 weeks plus 2 or 3 days. Rats were individually exposed to test atmospheres in wire-mesh exposure cages in 4300-liter rectangular glass and stainless steel chambers with an airflow rate of approximately 900 liter/minute with 12.5 air changes/hour. Chamber temperature, relative humidity, and cumene concentration (measured by GC) were measured every half hour during the 6-hour exposure. When not in the exposure chambers, the rats were individually housed and maintained on a 12-hour photoperiod and had ad libitum access to basal rodent diet and water. During the study, cages were rotated within the exposure chamber and non-exposure housing to ensure uniform exposures to the test material and lighting. In addition to the parameters studied for the subchronic study, the epididymides of 15 male rats/group were removed to evaluate sperm count and sperm morphology. Also, the right testis of each male was frozen and homogenized to count spermatid by the method of Johnson et al. (1980) and Blazak et al. (1985). In the high-dose and control groups, the right testis of each male rat was evaluated for the stages of spermatogenesis according to the method of Land and Chapin (1985).
NOAEL(NOEL)	1200 ppm

Appropriate statistical evaluations	Yes. Levene's test for equal variances, ANOVA, t tests, repeated-measures analysis (Dixon, 1985), Fisher's exact test.
Parental data and F1 as Appropriate	Testicular sperm head and epididymal spermatozoa counts were similar for all groups. At 1,200 ppm, one rat was reported to show diffuse testicular atrophy; however, all other animals showed normal morphology and stages of spermatogenesis in the testes. In epididymal spermatozoa, there were no individual abnormalities of the sperm head; however, at 500 ppm, when total abnormalities where grouped by total number per category, there appeared to be a slight increase (statistical significance not reported) in the incidence of head abnormalities. No effects on epididymal sperm morphology were reported based on more than 96% normal epididymal sperm.
Remarks for Results	The slight increase in total head abnormalities noted at 500 ppm were considered by the authors to be irrelevant since no dose-response was observed and when evaluated as percentage of sperm assessed, sperm head abnormalities were infrequent. In addition, no statistical significance was reported by the authors.
Data Reliabilities Qualities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Cushman J.R., Norris, J.C., Dodd, D.E., Darmer, K.I., Morris, C.R. (1995) Subchronic inhalation toxicity and neurotoxicity assessment of cumene in Fischer 344 rats. J Am Coll Toxicol., 14(2),129-147.

4.5 Developmental/Teratogenicity Toxicity

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue cumene, purity greater than 99.9%
Test Type	Developmental toxicity
GLP	Ambiguous
Year	1997
Species/strain	Rat/CD
Sex	Female
Route of Administration	Inhalation
Duration of Test	21 days
Doses/concentration Levels	100, 500, or 1,200 ppm

Exposure Period	Gestation days 6-15
Frequency of Treatment	6 hours/day
Control Group and Treatment	0 ppm
Remarks for Test Conditions	Male and female CD rats (60 days of age) were quarantined for 2 weeks and when deemed suitable for study, were mated (1 male to 1 female). Groups of 25 plug-positive females were exposed to atmospheres containing 0, 100, 500, or 1,200 ppm cumene 6 hours/day during gestation days 6-15. Rats were individually exposed to test atmospheres in wire-mesh exposure cages in 4,320-liter rectangular glass and stainless steel chambers with an airflow rate of approximately 900 liters/minutes with 14 air changes/hour and a theoretically derived time required for the chamber to reach 99% of the equilibrium concentration (t99) of approximately 20 min. Atmospheric pressure in the chambers was maintained at a slightly negative pressure to prevent possible leaks. Chamber temperature, relative humidity, cumene concentration (measured by GC) and airflow were measured every half hour during the 6-hour exposure. When not in the exposure chambers, the rats were individually housed and maintained on a 12-hour photoperiod and had ad libitum access to basal rodent diet and water. Rats were observed daily for clinical signs. Body weight and food consumption were measured on gestation days 0, 6, 9, 12, 15, 18, and 21. On gestation day 21, maternal rats were killed and the gravid uterus, ovaries (including corpora lutea), cervix, vagina, abdominal and thoracic cavities, and respiratory tracts (including nasal turbinates) were examined. Live and dead fetuses and resorption sites were recorded. Any nongravid uteri were placed in 10% ammonium sulfide solution for detection of early resorptions. Live fetuses were examined for gender, external malformations, and variations and skeletal malformations and variations. Fifty percent of the live fetuses were examined for thoracic and abdominal visceral abnormalities, and for craniofacial structures.
NOAEL(NOEL) maternal toxicity	488 ppm
LOAEL(LOEL) maternal toxicity	99 ppm
NOAEL (NOEL) developmental toxicity	1211 ppm
Actual dose received by dose level and sex	0, 99, 488, or 1,211 ppm
Maternal data with dose level	All rats survived to termination of study with no abortions or early deliveries. At 0, 100, and 500 ppm, 2, 2, and 3 rats were not pregnant. The pregnancy rate ranged from 88-100% and a total of 22-25 litters were examined for each group. During exposure, the high-dose rats showed significant reductions in body weight gain, but no significant differences in maternal body weight were reported when the rats were weighed. At both 500 and 1,200 ppm, food consumption was significantly reduced during the exposure period. At the highest concentration, perioral wetness, encrustation, and significantly increased relative liver weight were reported. There were no

	increased relative liver weight were reported. There were no effects noted at necropsy and no significant changes in maternal corrected gestational weight, gravid uterine weight, or absolute liver weight in any of the treatment groups.
Fetal Data with Dose Level	No statistically significant effects were reported in the fetuses. Parameters examined included number of corpora lutea, number of total nonviable or viable implantations, percent pre- or post-implantation loss, sex ratio, fetal body weights, malformations, or variations. Although there was a significant increase in the incidence of skeletal and visceral variations, they were not exposure related.
Appropriate statistical evaluations	Yes. Levene's test for equal variances, ANOVA, t tests, Kruskal-Wallis test, Mann-Whitney U test, Fisher's exact test.
Remarks for Results	In reviewing this study, EPA (1997) set the maternal NOAEL at 488 ppm based on the significant decrease in body weight gain during exposure and increased relative liver weight.
Conclusion Remarks	Even at maternally toxic concentrations, exposure to cumene vapor did not produce developmental toxicity.
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report which meets basic scientific principles.
References	Darmer K.I., Jr., Neeper-Bradley, T.L., Cushman, J.R., Morris, C.R., and Francis, B.O. (1997) Developmental toxicity of cumene vapor in CD rats and New Zealand white rabbits. Intl J Toxicol., 16, 119-139.

Substance Name	*p*-Cymene
CAS No.	99-87-6
Remarks for Substance	Data for homologue cumene, purity greater than 99.9%
Test Type	Developmental toxicity
GLP	Ambiguous
Year	1997
Species/strain	Rabbit/New Zealand white
Sex	Female
Route of Administration	Inhalation
Duration of Test	29 days
Doses/concentration Levels	500, 1,200, or 2,300 ppm
Exposure Period	Gestation days 6-18
Frequency of Treatment	6 hours/day
Control Group and Treatment	0 ppm
Remarks for Test Conditions	Male and female New Zealand white rabbits (5.5 months of age) were quarantined for 2 weeks and when deemed suitable for study, were mated (1 male to 2 female). Groups of 15 mated

	for study, were mated (1 male to 2 female). Groups of 15 mated females were exposed to atmospheres containing 0, 500, 1,200, or 2,300 ppm cumene 6 hours/day during gestation days 6-18. Rabbits were individually exposed to test atmospheres in wire-mesh exposure cages in 4,320-liter rectangular glass and stainless steel chambers with an airflow rate of approximately 900 liter/minutes with 14 air changes/hour and a theoretically derived time required for the chamber to reach 99% of the equilibrium concentration (t99) of approximately 20 min. Atmospheric pressure in the chambers was maintained at a slightly negative pressure to prevent possible leaks. Chamber temperature, relative humidity, cumene concentration (measured by GC) and airflow were measured every half hour during the 6-hour exposure. When not in the exposure chambers, the rabbits were individually housed and maintained on a 12-hour photoperiod and had ad libitum access to basal rabbit diet and water. Rabbits were observed daily for clinical signs. Food consumption was measured daily and body weight was measured on gestation days 0, 6, 12, 18, 24, and 29. On gestation day 29, maternal rabbits were killed and the gravid uterus, ovaries (including corpora lutea), cervix, vagina, abdominal and thoracic cavities, and respiratory tracts (including nasal turbinates) were examined. Live and dead fetuses and resorption sites were recorded. Any nongravid uteri were placed in 10% ammonium sulfide solution for detection of early resorptions. Live fetuses were killed immediately upon removal were examined for gender, external malformations, and variations, skeletal malformations and variations, and thoracic and abdominal visceral abnormalities. Fifty percent of the fetuses were decapitated and examined for craniofacial structures.
NOAEL(NOEL) maternal toxicity	1,206 ppm
LOAEL(LOEL) maternal toxicity	2,297 ppm
NOAEL (NOEL) developmental toxicity	1,206 ppm
LOAEL (LOEL) developmental toxicity	2,297 ppm
Actual dose received by dose level and sex	0, 492, 1206 or 2297 ppm
Maternal data with dose level	Two does died and one aborted at the highest concentration. At the 2 lower concentrations, 1 doe in each group contained non-viable implants. All does in all groups were pregnant. During exposure, high-dose does had significantly reduced body weight gain and all treated animals had significantly reduced food consumption. The incidence of perioral wetness was significantly increased in high-dose does. At necropsy, no gross observations with the exception of lung color changes in 4/12 high-dose does were reported and there were no statistically significant differences in maternal body weight, maternal corrected gestational weight change, or absolute liver weight in any of the treatment groups. Relative liver weight was significantly increased in high-dose animals.
Fetal Data with Dose Level	No statistically significant effects were reported in the fetuses. Parameters examined included number of corpora lutea, number of total nonviable or viable implantations, percent pre-

	number of total nonviable or viable implantations, percent pre- or post-implantation loss, sex ratio, fetal body weights, malformations, or variations. Although there was a significant increase in the incidence of skeletal and visceral variations, they were not exposure related. At 500 ppm, there was a statistically significant increase in the incidence of ecchymosis (small hemorrhage) on the head, which was not significant at the higher exposure concentrations.
Appropriate statistical evaluations	Yes. Levene's test for equal variances, ANOVA, t tests, Kruskal-Wallis test, Mann-Whitney U test, Fisher's exact test.
Remarks for Results	The increased incidence of ecchymosis on the head reported at 500 ppm was considered by the authors to be consistent with historical values. In further review of this study, EPA (1991) determined that the changes in gestational parameters, though not significant, were consistent in indicating possible developmental effects and therefore set the NOAEL for both developmental and maternal effects at 1206 ppm and the LOAEL at 2297 ppm (as reported in EPA, 1997).
Data Qualities Reliabilities	Reliability code 2. Reliable with restriction.
Remarks for Data Reliability	Code 2. Acceptable, well-documented publication/study report, which meets basic scientific principles.
References	Darmer K.I., Jr., Neeper-Bradley, T.L., Cushman, J.R., Morris, C.R., and Francis, B.O. (1997) Developmental toxicity of cumene vapor in CD rats and New Zealand white rabbits. Intl J Toxicol., 16, 119-139.